6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie E. Reeves, Ph.D. whose telephone number is (703) 308-7553.

Julie C Reeves

Julie E. Reeves, Ph.D.

JULIE REEVES
PATENT EXAMINER

Interview Summary

Application No.	Applicant(s)
08/146,206	Carter et al
Examiner	**Group Art Unit**
Julie E. Reeves, Ph.D.	1642

All participants (applicant, applicant's representative, PTO personnel):

(1) *Julie E. Reeves, Ph.D.* (3) _____

(2) *Wendy Lee* (4) _____

Date of Interview *Jan 7, 1999*

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: *all pending*

Identification of prior art discussed:
none

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Applicant indicated that they intend to file a supplemental amdt.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

JULIE REEVES
PATENT EXAMINER

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

#49

Official Document - *GENENTECH, INC.*

1 DNA Way, South San Francisco, CA 94080-4990 Tel: 650-225-7039 Fax: 650-952-9881

FAX TRANSMISSION COVER SHEET

Date: April 9, 1999

To: Examiner J. Reeves *Group Art Unit: 1642 of US PTO*

Fax: (703)308-4426

Re: U.S. Ser. No 08/146,206 *filed November 17, 1993* *(Attorney Docket No.: P0709P1)*

Sender: Wendy M. Lee

CERTIFICATION OF FACSIMILE TRANSMISSION
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.
Ann Savelli
Type or print name of person signing certification
Ann Savelli 4/9/99
Signature Date

YOU SHOULD RECEIVE 2 PAGES, INCLUDING THIS COVER SHEET. IF YOU DO NOT RECEIVE ALL THE PAGES, PLEASE CALL 650-225-7039

Comments:

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE #49

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: J. Reeves

Response to Restriction Requirement

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action dated March 29, 1999 and pursuant to the telephonic conversation between the undersigned and Examiner Reeves of today's date, Applicants hereby elect the species 78H ("Species AA" and "Species JJ"), with traverse. Claims readable on the elected species include claims 72-75, 102, 104, 105, 115-118, 122 and 124-127. Applicants traverse the restriction requirement to the extent that 37 CFR 1.129(b)(1) states that in applications such as the present application (which had been pending for at least three years as of June 8, 1995 taking into account reference made in the application under 35 USC 120 to USSN 07/715,272 filed June 14, 1991), "no requirement for restriction or for the filing of divisional applications shall be made or maintained in the application after June 8, 1995".

Respectfully submitted,
GENENTECH, INC.

Date: April 9, 1999

By: _____
Wendy M. Lee
Reg. No. 40,378

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

Supp. #5
6/11/99

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: Julie Burke

COMMUNICATION

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

As requested by Examiner Julie Burke enclosed is the specification for USSN 07/715,272 (now abandoned) which is the priority document for the above-identified patent application.

Respectfully submitted,
GENENTECH, INC.

By: _____
Wendy M. Lee
Reg. No. 40,378

Date: June 9, 1999

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

Interview Summary

Application No.	Applicant(s)
08/146,206	Carter et al
Examiner	**Group Art Unit**
Julie E. Burke, (Reeves), Ph.D.	1642

All participants (applicant, applicant's representative, PTO personnel):

(1) *Julie E. Burke, (Reeves), Ph.D.* (3) _____

(2) *Wendy Lee* (4) _____

Date of Interview *16 Jul 1999*

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: *all pending*

Identification of prior art discussed:
none in detail

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Examiner phoned to say the claims 43-44, 46-73, 75-105, 115-127 are in condition for allowance; claims 45, 74, 117 are objected to for not further limiting the independent claims; claims 111-112 are double patenting with claims reciting the VH subgroup III heavy chain consensus region, as allowed in 08/437,642, accordingly a terminal disclaimer is necessary for the allowance of claims 111-112; claims 106-110, 113-114 and 128 need further prosecution. Applicant elected to not procede with the allowance at this time. A supplemental amdt will be filed today and an interview has been scheduled 23rd August.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

JBurke

JULIE BURKE
PRIMARY EXAMINER

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

7/16/99 *Official Document* · **GENENTECH, INC.** #51

1 DNA Way, South San Francisco, CA 94080-4990 Tel: 650-225-7039 Fax: 650-952-9881

FAX TRANSMISSION COVER SHEET

Date: July 16, 1999

To: Examiner Julie Burke Group Art Unit: 1642 of US PTO

Fax: (703) 308-4426

Re: U.S. Ser. No 08/146,206 filed November 17, 1993 (Attorney Docket No.: P0709P1)

Sender: Wendy M. Lee

CERTIFICATION OF FACSIMILE TRANSMISSION
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Wendy Lee
Type or print name of person signing certification

W M Lee 7/16/99
Signature *Date*

YOU SHOULD RECEIVE 2 PAGE(S), INCLUDING THIS COVER SHEET. IF YOU DO NOT RECEIVE ALL THE PAGES, PLEASE CALL 650-225-7039

Comments:

Paper #51 Amdt K

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE 7/16/99 9e

In re Application of	Group Art Unit: 1642
Paul J. Carter et al.	Examiner: J. Burke
Serial No.: 08/146,206	
Filed: November 17, 1993	
For: METHOD FOR MAKING HUMANIZED ANTIBODIES	

SUPPLEMENTAL AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Further to the Supplemental Amendment dated January 15, 1999, please amend the present application as follows:

IN THE CLAIMS:

In line 3 of claims 43 and 115, please replace "further comprising an" with --further comprising a Framework Region (FR)--.

In line 4 of claim 72 please replace "further comprises an" with --further comprises a Framework Region (FR)--.

REMARKS

For claim precision, claims 43, 72 and 115 now refer to a Framework Region (FR) substitution, which provides anticedence for Framework Region (FR) in the claims which depend thereon.

Respectfully submitted,
GENENTECH, INC.

Date: July 16, 1999

By: _____
Wendy M. Lee
Reg. No. 40,378

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: Julie Burke

CERTIFICATE OF FACSIMILE TRANSMISSION

Aug. 30, 1999 : Date of Transmission

I hereby certify that this correspondence, consisting of a Supplemental Amendment, is being facsimile transmitted to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Ann Savelli

Ann Savelli

SUPPLEMENTAL AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Further to the Supplemental Amendment dated July 16, 1999, please amend the present application as follows:

IN THE CLAIMS:

Please cancel claims 106-112, without prejudice.

In claim 113, line 9, after "one another", please insert --, wherein the humanized variant binds antigen up to about 3-fold more tightly than the parent antibody binds antigen--.

In claim 114, line 1, please delete "at least".

In claim 128, line 7, please insert --up to about 3-fold-- before "more tightly".

REMARKS

The undersigned confirms having met with Examiners Burke and Feisee in the interview August 23, 1999, and takes this opportunity to thank them for the courtesies extended in that interview.

As requested by Examiner Burke in the above interview, claims 113 and 128 have been revised, for claim precision, to refer to the humanized variant which binds antigen up to about 3-fold better than the parent antibody. Claims 113-114 and 128 have been revised herein in order to facilitate allowance of the present application and without acquiescing in any rejection. Basis for the revisions of these claims is found on at least page 70, lines 31-32 and in Table 3 on page 72. Aside from humanized anti-HER2 variants huMAb4D5-6 and huMAb4D5-8 in the present application, it is noted that humanized M195 has an affinity which is about 3-fold better than the parent antibody as recited in claim 128 (see first line on page 1153 of Co *et al. J. Immunol.* 148:1149-1154 (1992) (of record); and Caron *et al. Cancer Research* 52:6761-6767 (1992) (of record)).

To avoid the obviousness-type double patenting rejection of claim 111 over claim 47 of co-pending application USSN 08/437,642, Applicants have cancelled claims 111-112 herein, without prejudice to filing a continuing application directed thereto. In addition, in order to simplify prosecution, and without acquiescing in any objection or rejection, claims 106-110 have been cancelled. Applicants reserve the right to

file a continuing application directed to claims 106-110.

Examiner Burke suggested that claims 45, 74 and 117 be cancelled as not further limiting the independent claims on which they depend. The undersigned pointed out that, due to the use of the "comprising" language, claims 43, 72 and 115 clearly encompass humanized antibody variable domains or antibodies with one or more Framework Region (FR) substitutions, wherein at least one of those FR substitutions is set forth in the group of sites in the claims. Hence, claims 45, 74 and 117 are further limiting and need not be cancelled. The Examiner then asserted that, without an upper limit on the number of FR substitutions, independent claims 43, 72 and 115 could read on a prior art antibody with an intact murine variable domain. Applicants respectfully submit, in this regard, that given that these claims are directed to a "humanized" antibody variable domain or antibody, it is apparent that the claims cannot encompass antibodies with intact murine variable domains. This is apparent from page 2, lines 29-34 and page 10, lines 27-31.

Respectfully submitted,
GENENTECH, INC.

Date: August 30, 1999

By: _____
Wendy M. Lee
Reg. No. 40,378

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/146,206	11/17/93	CARTER P	709P1

HM22/1124

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO CA 94080-4990

EXAMINER	
BURKE, J	

ART UNIT	PAPER NUMBER
1642	33

DATE MAILED: 11/24/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

08/146,206

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/146,206 11/17/93 FITER P 709P1 VB

DEA/FCE-1994

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
		HM22/1124	

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO CA 94080-4990

BURKE, J

EXAMINER	
1642	
ART UNIT	PAPER NUMBER
	55

DATE MAILED: 11/24/99

Please find below a communication from the EXAMINER in charge of this application

Commissioner of Patents

1. Please see attachment.

2. Any inquiry concerning this communication should be directed to Examiner Julie E. Burke, née Reeves, Ph.D, Art Unit 1642, whose telephone number is (703) 308-7553.

JBurke

JULIE BURKE
PRIMARY EXAMINER

Attachment

~~DETAILED ACTION~~

98

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's second submission after final filed on 8/26/98 has been entered.

2. The amendment to claim 113, filed 8/30/97 as Amendment L, Paper no 54 is not in compliance with 37 CFR 1.121 because more than five words are included in the amendment to the claim.

3. The application is not in compliance with the Sequence Requirements for the reasons set forth on the attached raw sequence listing error report. In brief, the application contains a new paper copy of the sequence listing containing 30 sequences, which was added by amendment G filed 10/7/97. The computer readable form of the sequences filed on the same day has only 26 sequences. Therefore the statements on page 3 of Paper no 32 filed 10/7/97 that the paper copy and computer readable form are the same is not sufficient. Additionally, it is not clear which new sequences have been added to the application, whether these sequences are new matter or whether the new sequences have unique SEQ ID NO:s.

4. Since the above-mentioned reply appears to be *bona fide*, and (1) in order to allow applicant the opportunity to amend the claims as they intend and (2) to complete the application with regards to Sequence Requirements, applicant is given a TIME PERIOD of **ONE (1) MONTH** or **THIRTY (30) DAYS**, from the mailing date of this notice, whichever is longer,

within which to supply the omission or correction in order to avoid abandonment.

EXTENSIONS OF THIS TIME LIMIT MAY BE GRANTED UNDER 37 CFR 1.136(a).

5. In an interest to complete the record of which papers have been entered in to the application, the following section is enclosed.

6. Claims 1-8, 10-12, 15 and 22-42 have been canceled and claims 43-114 added by Amendment H filed 9/26/98 as paper no 39 along with the Shak Declaration under 1.132.

7. Claims 43, 72, 104-106 and 112 have been amended by Amendment I, filed 11/6/98 as paper no 42.

8. Claims 43-44, 72-73, 104-106, 113-114 have been amended and claims 115-128 added by Amendment J filed 1/15/99 as Paper no 44.

9. Claims 43 and 72 have been amended By amendment K filed 7/16/99 as paper no 51.

10. Claims 106-112 have been canceled, claims 114 and 128 amended by amendment L field 8/30/99 as paper no 54. Please note in view of the noncompliance with 37 CFR 1.121, the amendment to claim 113 has not been entered.

11. Claims 43-105, 113-128 are pending and under examination.

12. It is noted that the Restriction Requirement set forth in Paper no 48 mailed 3/29/99 has been withdrawn in view of the arguments set forth in Paper no 49 filed 4/9/99.

13. Once the application is in compliance with the Sequence Requirements and the claims are amended as applicant's intended, the claims will be examined for their merits.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie E. Burke, née Reeves, Ph.D, whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

JBurke

Julie E. Burke, née Reeves, Ph.D.

Primary Patent Examiner

(703) 308-7553

JULIE BURKE
PRIMARY EXAMINER

WD

Attorney Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: J. Burke CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on December 22, 1999 Ann Savelli Ann Savelli

SUPPLEMENTAL AMENDMENT AND RESPONSE TO OFFICE COMMUNICATION

#56/M

KD 1-11-00

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Responsive to the communication dated November 24, 1999, please amend the present application as follows:

IN THE SPECIFICATION:

On page 9, line 16, please replace "(I)" with --(•)--.

On page 9, line 16, please replace "(n)" with --(○)--.

On page 9, line 17, please replace "(I)" with --(□)--.

On page 62, line 3, please replace "12301 Parklawn Drive, Rockville, MD" with --10801 University Blvd., Manassas, VA--.

On page 84, line 3, please replace "(Rockville, MD)" with --(Manassas, VA)--.

M

Please replace the existing sequence listing in the specification with the attached sequence listing (pages 90-105).

IN THE CLAIMS:

Please amend claim 113 as follows:

113. (Twice Amended) A humanized variant of a non-human parent antibody which binds an antigen with better affinity than the parent antibody and comprises a consensus human variable domain of a human heavy chain immunoglobulin subgroup wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another, wherein the humanized variant binds antigen up to about 3-fold more tightly than the parent antibody binds antigen.

REMARKS

In the above communication, the Examiner states that the amendment to claim 113 filed 8/30/99 (Paper # 54) was not in compliance with 37 CFR 1.121. Accordingly, claim 113 is amended herein in a manner which complies with 37 CFR 1.121. Comments in paragraph 2 on page 2 of the 8/30/99 amendment with respect to the amendment of claim 113 are incorporated herein.

The Examiner further states in the above communication that the substitute sequence listing filed 10/7/97 is not in compliance with the sequence requirements. Applicants submit that their records indicate that the content of the CRF of the sequence listing filed 10/7/97 was indeed the same as the paper copy of that sequence listing filed 10/7/97. Nevertheless, a replacement sequence listing (paper copy and CRF) are filed herewith. In accordance with 37 CFR §§ 1.821 (f) and (g), the undersigned hereby states (a) that the content of the paper and computer readable sequence listings submitted herewith is the same; and (b) that this submission includes no new matter.

With respect to the attached sequence listing, Applicants point out that due to the nonprejudicial cancellation of claim 41 (which referred to SEQ ID NO's 27-30) in the 8/24/98 amendment, SEQ ID NO's 27-30 have been removed from the sequence listing filed herewith.

For the Examiner's convenience, Applicants will summarize here the differences between the presently-filed sequence listing, and the originally-filed (11/17/93) sequence listing:

1. SEQ ID NO:4 was corrected 10/7/97 to correspond to the HUV_HIII sequence in Fig. 1B.
2. SEQ ID NO:19 was corrected 6/2/94 to correspond to the muxCD3 sequence in Fig. 5.
3. SEQ ID NO:23 was amended 6/2/94 to correspond to the pH52-8.0 sequence in Fig. 6A.
4. SEQ ID NO:26 was added 9/2/97 for the huxCD3v1 sequence in Fig. 5.

Corrections to the specification have been made hereinabove as follows: The symbols from Fig. 3 have been corrected on page 9; and the ATCC address has been updated on pages 62 and 84. Applicants submit that no new matter is added by these amendments.

Further prosecution on the merits is anxiously awaited. Should the Examiner have any questions concerning this submission, she is invited to call the undersigned at the number noted below.

Respectfully submitted,
GENENTECH, INC.

Date: December 22, 1999

By: WM Lee
Wendy M. Lee
Reg. No. 40,378

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

3

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Carter, Paul J.
Presta, Leonard G.

(ii) TITLE OF INVENTION: Method for Making Humanized Antibodies

(iii) NUMBER OF SEQUENCES: 26

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genentech, Inc.
(B) STREET: 1 DNA Way
(C) CITY: South San Francisco
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 94080

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: WinPatin (Genentech)

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: 08/146206
(B) FILING DATE: 17-Nov-1993
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/715272
(B) FILING DATE: 14-JUN-1991

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Lee, Wendy M.
(B) REGISTRATION NUMBER: 40,378
(C) REFERENCE/DOCKET NUMBER: P0709P1

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 650/225-1994
(B) TELEFAX: 650/952-9881

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
 1               5                  10                  15

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn
            20                  25                  30
```

```
Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
                35                  40                  45

Leu Leu Ile Tyr Ser Ala Ser Phe Leu Glu Ser Gly Val Pro Ser
                50                  55                  60

Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile
                65                  70                  75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                80                  85                  90

His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
                95                 100                 105

Ile Lys Arg Thr
            109
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
  1               5                  10                  15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys
                20                  25                  30

Asp Thr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
                35                  40                  45

Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr
                50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser
                65                  70                  75

Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
                80                  85                  90

Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
                95                 100                 105

Ala Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
               110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
 1               5                  10                  15

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser
            20                  25                  30

Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
            35                  40                  45

Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser
            50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
            65                  70                  75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            80                  85                  90

Tyr Asn Ser Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu
            95                 100                 105

Ile Lys Arg Thr
        109
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1               5                  10                  15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
            20                  25                  30

Asp Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            35                  40                  45

Glu Trp Val Ala Val Ile Ser Glu Asn Gly Ser Asp Thr Tyr Tyr
            50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
            65                  70                  75

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            80                  85                  90

Thr Ala Val Tyr Tyr Cys Ala Arg Asp Arg Gly Gly Ala Val Ser
            95                 100                 105

Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
           110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val
 1               5                  10                  15

Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn
            20                  25                  30

Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly His Ser Pro Lys
            35                  40                  45

Leu Leu Ile Tyr Ser Ala Ser Phe Arg Tyr Thr Gly Val Pro Asp
            50                  55                  60

Arg Phe Thr Gly Asn Arg Ser Gly Thr Asp Phe Thr Phe Thr Ile
            65                  70                  75

Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
            80                  85                  90

His Tyr Thr Thr Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu
            95                 100                 105

Ile Lys Arg Ala
           109
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
 1               5                  10                  15

Ala Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys
            20                  25                  30

Asp Thr Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
            35                  40                  45

Glu Trp Ile Gly Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr
            50                  55                  60

Asp Pro Lys Phe Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser
            65                  70                  75
```

Ser Asn Thr Ala Tyr Leu Gln Val Ser Arg Leu Thr Ser Glu Asp
80 85 90

Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
95 100 105

Ala Met Asp Tyr Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
110 115 120

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TCCGATATCC AGCTGACCCA GTCTCCA 27

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GTTTGATCTC CAGCTTGGTA CCHSCDCCGA A 31

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AGGTSMARCT GCAGSAGTCW GG 22

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TGAGGAGACG GTGACCGTGG TCCCTTGGCC CCAG 34

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GTAGATAAAT CCTCTAACAC AGCCTATCTG CAAATG 36

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GTAGATAAAT CCAAATCTAC AGCCTATCTG CAAATG 36

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GTAGATAAAT CCTCTTCTAC AGCCTATCTG CAAATG 36

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 68 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTTATAAAGG TGTTTCCACC TATAACCAGA AATTCAAGGA TCGTTTCACG 50

ATATCCGTAG ATAAATCC 68

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CTATACCTCC CGTCTGCATT CTGGAGTCCC 30

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
1 5 10 15

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Arg
20 25 30

Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys
35 40 45

Leu Leu Ile Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser
50 55 60

Lys Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
65 70 75

Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
80 85 90

Gly Asn Thr Leu Pro Trp Thr Phe Ala Gly Gly Thr Lys Leu Glu
95 100 105

Ile Lys
107

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg
20 25 30

Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
35 40 45

Leu Leu Ile Tyr Tyr Thr Ser Arg Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Gly Asn Thr Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys
107

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser
20 25 30

Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
35 40 45

Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Tyr Asn Ser Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys
107

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 122 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
 1               5                  10                  15

Ala Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr
            20                  25                  30

Gly Tyr Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu
        35                  40                  45

Glu Trp Met Gly Leu Ile Asn Pro Tyr Lys Gly Val Ser Thr Tyr
    50                  55                  60

Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser
65                  70                  75

Ser Ser Thr Ala Tyr Met Glu Leu Leu Ser Leu Thr Ser Glu Asp
            80                  85                  90

Ser Ala Val Tyr Tyr Cys Ala Arg Ser Gly Tyr Tyr Gly Asp Ser
        95                  100                 105

Asp Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val
    110                 115                 120

Ser Ser
    122
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 122 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1               5                  10                  15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ser Phe Thr
            20                  25                  30

Gly Tyr Thr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
        35                  40                  45

Glu Trp Val Ala Leu Ile Asn Pro Tyr Lys Gly Val Ser Thr Tyr
    50                  55                  60

Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ser
65                  70                  75

Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            80                  85                  90

Thr Ala Val Tyr Tyr Cys Ala Arg Ser Gly Tyr Tyr Gly Asp Ser
        95                  100                 105
```

```
Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val
                110                 115                 120

Ser Ser
    122
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 122 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1               5                  10                  15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
            20                  25                  30

Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            35                  40                  45

Glu Trp Val Ser Val Ile Ser Gly Asp Gly Gly Ser Thr Tyr Tyr
            50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
            65                  70                  75

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            80                  85                  90

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Val Gly Tyr Ser Leu
            95                 100                 105

Ser Gly Leu Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
           110                 115                 120

Ser Ser
    122
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 454 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
 1               5                  10                  15

Ala Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr
            20                  25                  30
```

Glu Tyr Thr Met His Trp Met Lys Gln Ser His Gly Lys Ser Leu
35 40 45

Glu Trp Ile Gly Gly Phe Asn Pro Lys Asn Gly Gly Ser Ser His
50 55 60

Asn Gln Arg Phe Met Asp Lys Ala Thr Leu Ala Val Asp Lys Ser
65 70 75

Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp
80 85 90

Ser Gly Ile Tyr Tyr Cys Ala Arg Trp Arg Gly Leu Asn Tyr Gly
95 100 105

Phe Asp Val Arg Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val
110 115 120

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
125 130 135

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
140 145 150

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
155 160 165

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
170 175 180

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
185 190 195

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
200 205 210

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
215 220 225

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
230 235 240

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
260 265 270

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
275 280 285

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
290 295 300

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305 310 315

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
320 325 330

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
335 340 345

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
350 355 360

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
365 370 375

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
380 385 390

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
395 400 405

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
410 415 420

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
425 430 435

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
440 445 450

Ser Pro Gly Lys
454

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 469 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr
1 5 10 15

Gly Val His Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly
35 40 45

Tyr Thr Phe Thr Glu Tyr Thr Met His Trp Met Arg Gln Ala Pro
50 55 60

Gly Lys Gly Leu Glu Trp Val Ala Gly Ile Asn Pro Lys Asn Gly
65 70 75

Gly Thr Ser His Asn Gln Arg Phe Met Asp Arg Phe Thr Ile Ser
80 85 90

Val Asp Lys Ser Thr Ser Thr Ala Tyr Met Gln Met Asn Ser Leu
95 100 105

Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Trp Arg Gly
110 115 120

Leu Asn Tyr Gly Phe Asp Val Arg Tyr Phe Asp Val Trp Gly Gln
125 130 135

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
140 145 150

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
155 160 165

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
170 175 180

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
185 190 195

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
200 205 210

Val Val Thr Val Thr Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
215 220 225

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
230 235 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
245 250 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
260 265 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
290 295 300

Val Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
305 310 315

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
320 325 330

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
335 340 345

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
350 355 360

Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
365 370 375

```
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
                380                 385                 390

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
                395                 400                 405

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
                410                 415                 420

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                425                 430                 435

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
                440                 445                 450

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                455                 460                 465

Ser Pro Gly Lys
            469
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 214 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
Asp Val Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
 1               5                  10                  15

Gly Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Asp Ile Asn
                20                  25                  30

Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asn Gly Thr Val Lys
                35                  40                  45

Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser
                50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
                65                  70                  75

Ser Asn Leu Asp Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
                80                  85                  90

Gly Asn Thr Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu
                95                 100                 105

Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
                110                 115                 120

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
                125                 130                 135
```

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
140 145 150

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu
155 160 165

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
170 175 180

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
185 190 195

Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
200 205 210

Arg Gly Glu Cys
214

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 233 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr
1 5 10 15

Gly Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
20 25 30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Asp Ile Asn Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
50 55 60

Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser
65 70 75

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr
80 85 90

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
95 100 105

Tyr Cys Gln Gln Gly Asn Thr Leu Pro Pro Thr Phe Gly Gln Gly
110 115 120

Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe
125 130 135

Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
140 145 150

```
Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
                155                 160                 165

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
                170                 175                 180

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                185                 190                 195

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
                200                 205                 210

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
                215                 220                 225

Lys Ser Phe Asn Arg Gly Glu Cys
                230         233
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 122 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1               5                  10                  15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ser Phe Thr
            20                  25                  30

Gly Tyr Thr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            35                  40                  45

Glu Trp Val Ala Leu Ile Asn Pro Tyr Lys Gly Val Thr Thr Tyr
            50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Val Asp Lys Ser
            65                  70                  75

Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            80                  85                  90

Thr Ala Val Tyr Tyr Cys Ala Arg Ser Gly Tyr Tyr Gly Asp Ser
            95                  100                 105

Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val
            110                 115                 120

Ser Ser
    122
```

RAW SEQUENCE LISTING
PATENT APPLICATION *US/08/146,206C*

This Raw Listing contains the General Information Section and up to the first 5 pages

SEQUENCE LISTING

(1) General Information:

(i) APPLICANT: Carter, Paul J.
Presta, Leonard G.

(ii) TITLE OF INVENTION: Method for Making Humanized Antibodies

(iii) NUMBER OF SEQUENCES: 26

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genentech, Inc.
(B) STREET: 1 DNA Way
(C) CITY: South San Francisco
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 94080

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: WinPatin (Genentech)

(vi) CURRENT APPLICATION DATA:
--> **(A) APPLICATION NUMBER: 08/146206**
(B) FILING DATE: 17-Nov-1993
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/715272
(B) FILING DATE: 14-JUN-1991

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Lee, Wendy M.
(B) REGISTRATION NUMBER: 40,378
(C) REFERENCE/DOCKET NUMBER: P0709P1

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 650/225-1994
(B) TELEFAX: 650/952-9881

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids

(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
 1               5                  10                  15

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn
            20                  25                  30

Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
        35                  40                  45

Leu Leu Ile Tyr Ser Ala Ser Phe Leu Glu Ser Gly Val Pro Ser
    50                  55                  60

Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile
65                  70                  75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                80                  85                  90

His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
            95                  100                 105

Ile Lys Arg Thr
        109
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1               5                  10                  15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys
            20                  25                  30

Asp Thr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
        35                  40                  45

Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr
    50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser
65                  70                  75
```

```
100   Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
101                    80                  85                  90
102
103   Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
104                    95                 100                 105
105
106   Ala Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
107                   110                 115                 120
108
109   (2) INFORMATION FOR SEQ ID NO:3:
110
111      (i) SEQUENCE CHARACTERISTICS:
112          (A) LENGTH: 109 amino acids
113          (B) TYPE: Amino Acid
114          (D) TOPOLOGY: Linear
115
116     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:
117
118   Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
119     1               5                  10                  15
120
121   Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser
122                    20                  25                  30
123
124   Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
125                    35                  40                  45
126
127   Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser
128                    50                  55                  60
129
130   Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
131                    65                  70                  75
132
133   Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
134                    80                  85                  90
135
136   Tyr Asn Ser Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu
137                    95                 100                 105
138
139   Ile Lys Arg Thr
140              109
141
142   (2) INFORMATION FOR SEQ ID NO:4:
143
144      (i) SEQUENCE CHARACTERISTICS:
145          (A) LENGTH: 120 amino acids
146          (B) TYPE: Amino Acid
147          (D) TOPOLOGY: Linear
148
149     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:
150
151   Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
152     1               5                  10                  15
```

```
153
154   Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
155                   20                  25                  30
156
157   Asp Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
158                   35                  40                  45
159
160   Glu Trp Val Ala Val Ile Ser Glu Asn Gly Ser Asp Thr Tyr Tyr
161                   50                  55                  60
162
163   Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
164                   65                  70                  75
165
166   Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
167                   80                  85                  90
168
169   Thr Ala Val Tyr Tyr Cys Ala Arg Asp Arg Gly Gly Ala Val Ser
170                   95                 100                 105
171
172   Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
173                  110                 115                 120
174
175   (2) INFORMATION FOR SEQ ID NO:5:
176
177      (i) SEQUENCE CHARACTERISTICS:
178          (A) LENGTH: 109 amino acids
179          (B) TYPE: Amino Acid
180          (D) TOPOLOGY: Linear
181
182     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:
183
184   Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val
185     1               5                  10                  15
186
187   Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn
188                   20                  25                  30
189
190   Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly His Ser Pro Lys
191                   35                  40                  45
192
193   Leu Leu Ile Tyr Ser Ala Ser Phe Arg Tyr Thr Gly Val Pro Asp
194                   50                  55                  60
195
196   Arg Phe Thr Gly Asn Arg Ser Gly Thr Asp Phe Thr Phe Thr Ile
197                   65                  70                  75
198
199   Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
200                   80                  85                  90
201
202   His Tyr Thr Thr Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu
203                   95                 100                 105
204
205   Ile Lys Arg Ala
```

206 109

207

208 (2) INFORMATION FOR SEQ ID NO:6:

209

210 (i) SEQUENCE CHARACTERISTICS:
211 (A) LENGTH: 120 amino acids
212 (B) TYPE: Amino Acid
213 (D) TOPOLOGY: Linear

214

215 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

216

217 Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
218 1 5 10 15

219

220 Ala Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys
221 20 25 30

222

223 Asp Thr Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
224 35 40 45

225

226 Glu Trp Ile Gly Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr
227 50 55 60

228

229 Asp Pro Lys Phe Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser
230 65 70 75

231

232 Ser Asn Thr Ala Tyr Leu Gln Val Ser Arg Leu Thr Ser Glu Asp
233 80 85 90

234

235 Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
236 95 100 105

237

238 Ala Met Asp Tyr Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
239 110 115 120

240

241 (2) INFORMATION FOR SEQ ID NO:7:

242

243 (i) SEQUENCE CHARACTERISTICS:
244 (A) LENGTH: 27 base pairs
245 (B) TYPE: Nucleic Acid
246 (C) STRANDEDNESS: Single
247 (D) TOPOLOGY: Linear

248

249 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

250

SEQUENCE VERIFICATION REPORT
PATENT APPLICATION *US/08/146,206C*

DATE: 01/20/2000
TIME: 01:04:05

INPUT SET: S34518.raw

Line	Error	Original Text
27	Wrong application Serial Number	(A) APPLICATION NUMBER: 08/146206

UNITED STATES DEPARTMENT OF COMMERCE
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Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/146,206	11/17/93	CARTER	P 709P1

HM22/1025

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO CA 94080-4990

EXAMINER	
DAVIS,M	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/146,206	Applicant(s)
	Examiner	Group Art Unit 1642

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 8/30/99.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 43-105, 113-128 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 43-105, 113-128 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other_____

Office Action Summary

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.129(a). Applicant's amendment filed on 08/26/98 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 106-112, and adds new claims 115-128, which are related to claims 43-105, and are not new matter.

Accordingly, claims 43-105, 113-128 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112 FIRST PARAGRAPH, SCOPE, NEW REJECTION

Claims 43-105, 113-128 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized antibody muMAb4D5, and an anti-CD3 antibody, or variable domains thereof, comprising CDR amino acids which bind specifically to p185, or CD3, does not reasonably provide enablement for any humanized antibody , or variable

domain thereof, comprising CDR amino acids which binds non-specifically to any antigen, wherein the framework region amino acids are substituted at a site selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, or of 24H, 73H, 76H, 78H and 93H, for treating any chronic diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 43-105, 113-128 are drawn to a humanized antibody , or variable domain thereof, comprising CDR amino acids which bind an antigen, or which bind $p185^{HER2}$. The framework region amino acids of said antibody or variable domain are substituted at a site selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, or of 24H, 73H, 76H, 78H and 93H. Claim 105 is further drawn to a humanized antibody which lacks immunogenicity upon repeated administration for treating a chronic disease, and wherein its non-human CDR amino acids bind an antigen.

The specification discloses examples of humanized antibody muMAb4D5, anti-CD3, and anti-CD18 antibody, or variable domain thereof, comprising CDR amino acids which bind specifically to p185, CD3, and CD18, respectively. The substituted framework residues for the heavy chain of antibody muMAb4D5 are amino acids number 71, 73, 78, 93, and for the light chains are amino acid number 66 (table 3, and p.68). Only one humanized antibody, huMab4D5-8,

with all of the above five substitutions in the framework region binds to p185 3-fold more tightly than the murine counterpart. The humanized antibodies, huMab4D5-2 and huMab4D5-3, with one and four substitutions in the framework region, respectively, are, however, at least 10-fold less potent than the murine counterpart, having a K_d of 4.7nM and 4.4nM, respectively, as compared to a K_d value of 0.30nM of the murine counterpart. The substituted framework residues for the heavy chain of antibody anti-CD3 are amino acids number 75 and 76. Although the specification discloses that humanized anti-CD3 antibody enhances the cytotoxic effects of cytotoxic T cells 4-fold against tumor cells expressing $p185^{HER2}$, there is no disclosure in the specification concerning the binding affinity of the humanized anti-CD3 or anti-CD18 as compared to the murine counterpart. The claims however encompass any humanized antibody, without any specificity, binding to $p185^{HER2}$ or any antigen, with just any one of substitution at a site selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, of 24H, 73H, 76H, 78H and 93H. The claims further encompass any humanized antibody for treating any chronic disease.

One cannot extrapolate from humanizing one antibody, which binds to $p185^{HER2}$ 3-fold more tightly than the murine counterpart, to humanizing any antibody, wherein its affinity would be up to 3-fold or at least 3-fold more tightly than the murine counterpart, or wherein its affinity would be still intact for therapeutic purposes. In addition, one cannot extrapolate from humanizing an anti-p185 antibody by substitution at all five framework amino acids number H71, H73, H78, H93 and L66 in an anti-p185 antibody, or from humanizing an anti-CD3 antibody by

substitution at both framework amino acids number H75 and H76 in an anti-CD3 antibody, with humanizing any antibody by substitution at only any one amino acid selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, or of 24H, 73H, 76H, 78H and 93H. Patent '101 teach that different antibodies require different combinations of different substitutions in the light chain and heavy chain (table 1). Even the specification discloses that only one variant, huMab4D5-8, wherein all five framework amino acids number H71, H73, H78, H93 and L66 are substituted, binds to p185 3-fold more tightly than the murine counterpart. Other variants, with only one or even four substitutions have much less binding affinity than the murine counterpart(table 3). Thus it is unpredictable that substitution at only one framework amino acid in any antibody, or any kind of combination of framework amino acid substitutions would result in a humanized antibody that binds to its antigen 3-fold more tightly than its murine counterpart, or retains adequate affinity for therapeutic purposes. The specification does not disclose whether subtitution at only one of the claimed amino acid positions would produce a humanized antibody that has 3-fold more in affinity as the murine counterpart, or retains adequate affinity for therapeutic purposes. The specification does not disclose which combination of what substituted framework amino acids, other than H71, H73, H78, H93 and L66 for anti-p185 antibody, and H75 and H76 in anti-CD3 antibody would produce a humanized antibody that has 3-fold more in affinity as the murine counterpart, or retains adequate affinity for therapeutic purposes. It is well known in the art that not any substitution at any amino acids would produce a humanized

antibody having an affinity similar to the murine counterpart, unless it is tested by binding assays. The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to make the claimed humanized antibodies with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Moreover, a humanized antibody that does not have a specificity for a particular antigen is of little practical use for treating a chronic disease, because said antibody would not target to the target tissues. In addition, although the specification discloses that murine anti-$p185^{HER2}$ antibody has been suceessfully used in treating tumor cell growth in culture (p.5), $p185^{HER2}$ and CD-3 are not specific for any tissues responsible for chronic disease, e.g. chronic headache, chronic lung inflammation, or chronic kidney disease. The specification does not disclose how to treat any chronic disease using the claimed humanized antibody. In the absence of a teaching of a method of treating any chronic disease, using the claimed humanized antibody, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 102, NEW REJECTION

1. New claims 115-117, 123, 127 are rejected under 35 USC 102(e) or 102(b) pertaining to anticipation by PN=5,530,101 or Queen et al, 1989, PNAS, USA, 86: 10029-10033.

Claims 115-117, 123, 127 are drawn to a humanized antibody or its heavy chain variable domain comprising non-human CDR amino acids, and a framework region amino acid wherein amino acid position 93H is substituted, utilizing the numbering system of Kabat, and wherein the substituted residue is the residue found in the corresponding location of the non-human antibody.

PN=5,530,101, teach humanized anti-Tac antibody, wherein amino acid 93 is substituted in heavy chain, using the aligned Kabat Eu sequence to provide the framework for the humanized antibody (column 45).

Queen et al, PNAS, teach humanized anti-Tac antibody, wherein amino acid 93 is substituted in heavy chain, using the aligned Kabat Eu sequence to provide the framework for the humanized antibody (figure 2).

Since anti-Tac antibody is a mouse antibody, its inherent heavy chain variable domain would comprise non-human CDR amino acids. Thus the humanized antibody and its heavy chain variable domain taught by patent '101 or Queen et al is the same as the claimed invention.

2. Claims 43, 44, 48, 55, 67, 71, 105, 115-117, 120, 127 are rejected under 35 USC 102(e) pertaining to anticipation by PN=5,530,101.

It is noted that PN=5,530,101 is filed on Sept, 1990, which is within a year before the claimed filing date of 06/14/91.

Claims 43, 44, 48, 55, 67, 71, 105, 115-117, 120, 127 are drawn to a humanized antibody or its heavy chain variable domain comprising non-human CDR amino acids, and a framework region amino acid wherein amino acid position 38L, 67L, 69H, 73H or 93H is substituted,

utilizing the numbering system of Kabat, and wherein the substituted residue is the residue found in the corresponding location of the non-human antibody. Claim 105 is further drawn to said humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient.

PN=5,530,101 teaches humanized antibodies, wherein amino acid 38 or 67 are substituted in light chain (table 1, antibody Fd79 and M195, respectively), and amino acid 69, 73 or 93 is substituted in heavy chain (table 1, antibody CMV5, mik-beta-1, and Fd138-80, respectively), using the aligned Kabat Eu sequence to provide the framework for the humanized antibody. The humanized antibodies in table 1 would comprise non-human CDR amino acids (Summary). Patent '101 further teaches that the humanized antibodies will be substantially non-immunogenic in humans (Abstract). Thus the humanized antibody taught by patent '101 and its variable domain is the same as the claimed invention.

REJECTION UNDER 35 USC 102

1. Claim 128 is rejected under 35 USC 102(e) as being anticipated by PN=5,530,101, for the same reasons set forth in paper No.27 for the rejection of previous claims 23-24.

Applicant amends the claim 128 to read that the humanized antibody binds the antigen up to about 3-fold more tightly than the parent antibody. The language "up to" 3-fold reads on anything below 3-fold. Thus the structure and binding affinity of the claimed humanized antibody is the same as that of the humanized antibody taught by '101.

2. Claim 113 is rejected under 35 USC 102(e) as being anticipated by PN=5,693,762, for the same reasons set forth in paper No.27 for the rejection of previous claims 22-25, 38 and 39.

Applicant argues that the "consensus sequence" in '762 is the most homologous sequence from a single human immunoglobulin, and is thus different from the consensus sequence of the claimed invention.

Applicant's arguments set forth in paper No. 39 have been considered but are not deemed to be persuasive for the following reasons:

Although '762 uses the most homologous sequence from a single human immunoglobulin as an example, '762 also teach that as a principle, a framework is used from either a human immunoglobulin which is unusually homologous to the donor immunoglobulin, **or** a consensus framework from many human antibodies is used (column 13, first paragraph, lines 4-7). Thus the consensus sequence taught by '762 is the same as the claimed consensus sequence, as defined by the specification, i.e. the most frequently occurring amino acids, based on immunoglobulin of a particular species (p.14).

REJECTION UNDER 35 USC 103

Claims 113, 115-118, 123, 127-128 are rejected under 35 USC 103 as being unpatentable over US PN=5,693,762 in view of Kabat et al, for the same reasons set forth in paper No:27, for the rejection of previous claims 26-36 and 40-41.

Applicant argues as follows:

The rejection is made using hindsight reconstruction of the present invention. Patent '762 actually teaches away from the invention. The term "consensus framework" from '762 patent was not intended to refer to a sequence representing the most frequently occurring amino acids in the present invention. Furthermore, Kabat et al do not use the term "consensus", but rather "occurrences of most common amino acid". Thus there is no motivation to combine "consensus framework" from '762 patent with "occurrences of most common amino acid", especially the term "consensus framework" from '762 patent was not intended to refer to a sequence representing the most frequently occurring amino acids. Moreover, the present invention produces humanized antibodies with unexpected results, such as 1) lack of significant immunogenecity, as disclosed in the Declaration by Dr. Shak, 2) higher increase in binding affinity as compared to that of humanized antibodies known in the art, and 3) the same consensus sequence could be used to generate many different strong affinity humanized antibodies.

Applicant's arguments set forth in paper No. 39 have been considered but are not deemed to be persuasive for the following reasons:

Although '762 uses the most homologous sequence from a single human immunoglobulin as an example, '762 also teach that **as a principle**, a framework is used from either a human immunoglobulin which is unusually homologous to the donor immunoglobulin, **or** use a consensus framework **from many human antibodies** is used (column 13, first paragraph, lines 4-7). Thus the consensus sequence taught by '762 is the same as the claimed consensus sequence, as defined by the specification, i.e. the most frequently occurring amino acids, based on immunoglobulin of a

particular species (p.14). It is only Applicant's interpretation that the term "consensus framework" from '762 patent was not intended to refer to a sequence representing the most frequently occurring amino acids in the present invention. Furthermore, although Kabat et al do not use the term "consensus", but rather "occurrences of most common amino acid", one of ordinary skill in the art would readily understand that " a consensus sequence" from many antibodies is a sequence that occurs most frequently.

In addition, .In re Kerkhoven (205 USPQ 1069, CCPA 1980) summarizes:

"It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose: idea of combining them flows logically from their having been individually taught in prior art."

Applicant asserts that the claimed humanized antibodies are not obvious in view of the cited references because the cited prior art does not suggest such a combination. However, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, given the teaching of the prior art that as a principle, a framework is used from either a human immunoglobulin which is unusually

homologous to the donor immunoglobulin, **or** a consensus framework from many human antibodies is used, and the structures of sequences that are most commonly occurred among many antibodies, it would have been obvious to humanize antibodies as taught by patent '762, using the most commonly occurred sequences taught by Kabat et al, because the idea of doing so would have logically followed from their having been individually taught in the prior art, and because patent '762 teaches the use of "consensus sequence", for the same purpose of producing humanized monoclonal antibodies for therapeutic purposes. One of ordinary skill in the art would have motivated to make humanized antibodies using the methods taught by '762 and the sequences taught by Kabat et al with a reasonable expectation of success. In addition, the arguments that the claimed invention is unexpected are not applicable, because the claims are broad, and drawn to any antibodies, and not specifically the claimed antibodies, wherein their specific target antigens, and their binding properties are not disclosed in the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

October 13, 2000

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Notice of References Cited

Application No.	Applicant(s)		
08/146,206	Carter et al.		
Examiner	Group Art Unit	Page 1 of 1	
M. T. Davis	1642		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
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FOREIGN PATENT DOCUMENTS

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	N						
	O						
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

*		DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
	U	~~Queen et al. PNAS, USA, 86: 10029 - 10033~~ Dupl.	~~1989~~
	V		
	W		
	X		

* A copy of this reference is not being funished with this Office action.
(See Manual of Patent Examining Procedure, Section 707.05(a).)

U.S. Patent and Trademark Office

Part of Paper No. 57

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: M. Davis CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on April 25, 2001 Wendy M. Lee

AMENDMENT UNDER 37 C.F.R. §1.111

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action dated 10/25/00, reconsideration of the present application is respectfully requested in view of the following amendments and remarks. A request for a 3 month extension of time and the requisite fee accompany this amendment.

IN THE CLAIMS:

Please amend claims 113 and 114 as follows:

113. (Amended) A humanized variant of a non-human parent antibody which binds an antigen and comprises a consensus human variable domain of a human heavy chain immunoglobulin subgroup wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with

respect to one another.

114. (Amended) The humanized variant of claim ~~128~~ which binds the antigen ~~about~~ up to 3-fold more ~~tightly~~ in the binding affinity than the parent antibody binds antigen.

REMARKS

Claims 43-105 and 113-128 are in the application. Claims 113 and 114 have been amended. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made".

Claim 113 no longer requires that the humanized variant bind antigen with better affinity than the parent antibody, up to about 3-fold tighter binding than the parent antibody. Hence, claim 114 has been amended herein to depend on claim 128, which claim requires that the humanized variant bind antigen more tightly than the parent antibody.

Prosecution History of the Present Application

Applicants first wish to express their concern about the undue prejudice to them due to the repeated transfer of this case from patent examiner to patent examiner, and to explain that this is a case which has thrice previously been indicated to be in condition for allowance.

The case was originally with Examiner Adams, then was transferred to Examiner Nolan. In the 8/13/98 interview, Examiner Nolan indicated that unexpected results would overcome the 103 rejection based on Queen Patent 5,693,762 (hereinafter "the '762 patent"). An amendment was filed 8/24/98 presenting the unexpected results. Shortly thereafter, the case was transferred to the present Examiner. Pending claims 43-114 were discussed in an interview on 10/16/98 between the undersigned, the present Examiner and Examiner Feisee at which time the only outstanding issue in the case related to the clarity of the terms "binding of CDR" and "significant immunogenicity". An amendment was filed 11/6/98 addressing those issues. The case was then transferred to Examiner Reeves, who issued a restriction requirement 3/29/99 at that late stage in prosecution. In an 8/23/99 interview, Examiners Reeves/Burke and Feisee indicated that the case would be in order for allowance with the filing of a terminal disclaimer for claim 111 and addition of an upper limit to affinity in claims 113 and 128. Claims 113 and 128 were amended as suggested by the Examiners and claim 111 was canceled to avoid the

obviousness-type double patenting rejection (see 8/30/99 amendment). Now the case has been transferred yet again to the present Examiner and prosecution has been re-opened on a case that was indicated to be in condition for allowance three times previously.

To the extent that any issues remain following entry of this amendment, Applicants specifically request an interview with the present Examiner and her supervisor to discuss this case so as to ensure speedy resolution of the issues and allowance of the application. It is noted that this is a pre-GATT case and two 129(a) responses have previously been filed.

Section 112, first paragraph, Scope, New Rejection

Claims 43-105 and 113-128 are rejected under 35 USC Section 112, first paragraph on the basis that the specification, while being enabling for humanized antibody muMAb4D5 and an anti-CD3 antibody, or variable domains thereof, "does not reasonably provide enablement for any humanized antibody, or variable domain thereof, comprising CDR amino acids which binds non-specifically to any antigen, wherein the framework region amino acids are substituted at a site selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H and 92H, or of 24H, 73H, 76H, 78H and 93H, for treating any chronic disease."

The Examiner contends that the specification discloses examples of humanized muMAb4D5, anti-CD3 and anti-CD18 antibodies or variable domains thereof; that the substituted FR residues for muMAb4D5 are 71H, 73H, 78H, 93H and 66L; and that only one humanized antibody (huMAb4D5-8) with all the above five substitutions binds to p185 3-fold more tightly than the murine counterpart. The Examiner further contends that the substituted framework residues for the heavy chain of antibody anti-CD3 are FR residues 75 and 76, and that there is no disclosure concerning the binding affinity of the humanized anti-CD3 or anti-CD18 as compared to the murine counterpart. The Examiner contends that one cannot extrapolate from humanizing one antibody, which binds to $p185^{HER2}$ 3-fold more tightly than the murine counterpart, to humanizing any antibody,

wherein its affinity would be up to 3-fold or at least 3-fold tighter than the murine counterpart, or wherein its affinity would still be intact for therapeutic purposes. The Examiner further argues that one cannot extrapolate from humanizing an anti-p185 antibody by substitution of all five FR residues at positions 71H, 73H, 78H, 93H and 66L in an anti-p185 antibody, or from humanizing an anti-CD3 antibody by substitution at both framework residues 75H and 76H, with humanizing any antibody by substitution at only one amino acid residue selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H and 92H, or of 24H, 73H, 76H, 78H and 93H. The Examiner opines that the specification does not disclose whether substitution at only one of the claimed amino acid positions would produce a humanized antibody that has 3-fold more affinity, or which combination of what substituted FR residues (other than 71H, 73H, 78H, 93H and 66L for an anti-p185 antibody or 75H and 76H in an anti-CD3 antibody) would produce a humanized antibody that has 3-fold more affinity than the murine counterpart, or retains adequate affinity for therapeutic purposes. The Examiner contends that a humanized antibody that does not have specificity for a particular antigen is of little practical use for treating a chronic disease and that the specification does not disclose how to treat any chronic disease using the claimed humanized antibody.

Applicants submit that claims 43-105 and 113-128 are enabled by the present application.

First, Applicants point out that none of the claims (other than claim 114) require that the humanized antibody bind antigen about 3-fold more tightly than the parent antibody binds antigen, as the Office Action seems to imply. The independent claims herein merely recite that the humanized antibody variable domain comprises CDR residues which bind an antigen (claims 43, 104 and 115); the antibody comprising the humanized antibody variable domain binds $p185^{HER2}$ (claim 72); the humanized antibody comprises CDR residues which bind an antigen (claim 105); the humanized variant bind antigen (claim 113 herein); or the humanized variant bind

antigen more tightly than the parent antibody - up to about 3-fold more tightly than the parent antibody (claim 128).

Second, Applicants submit that the claims herein encompass the humanized variable domain or antibody having at least one of the FR substitutions specified, but optionally having further FR substitution(s) in order to improve affinity to a level at which an antibody comprising the variable domain is able to bind antigen.

Finally, Applicants wish to clarify some issues concerning the Office's characterization of the working examples. First, it is noted that Example 1 actually describes several humanized anti-p185^{HER2} variants with FR substitution(s) as set forth in the claims herein: huMAb4D5-2, huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7, huMAb4D5-8 (Table 3 on page 72). Thus, it is clear that this example teaches humanized variants which do not include substitution of all of FR residues 71H, 73H, 78H, 93H and 66L. Each of these FR substitution variants bound antigen with better affinity than the initial antibody (huMAb4D5-1) comprising non-human CDR amino acid residues, but lacking any FR substitution(s). Two of the humanized anti-p185^{HER2} variants surprisingly bound antigen better than the murine parent antibody muMAb4D5, *i.e.* huMAb4D5-6 and huMAb4D5-8. With regard to Example 3 concerning the humanized anti-CD3 variants, aside from the 75H and 76H FR substitutions noted by the Office, this Example further teaches the following FR substitutions: L71, 71H, 73H and 78H. See, *e.g.*, Fig. 5 which aligns the murine anti-CD3 "muxCD3" sequences, the humanized variant "huxCD3v1" sequences, and the human sequences, "huκI" and "huIII".

The specification clearly teaches how to make humanized antibody variable domains and antibodies comprising such domains, and identifies FR residues that can be substituted to improve the binding affinity of an antibody comprising the humanized variable domain. See, *e.g.* pages 12-13, 20-26 and 28-29; Example 1 on pages 63-74; Example 3 on pages 79-88; and Example 4 on page 89. The specification teaches FR substitution(s)

individually or in combination. Based on the disclosure of the present application, one is able to make an antibody comprising a humanized antibody variable domain which binds antigen. The Office has provided no evidence that the humanized antibody variable domains or humanized antibodies comprising the FR substitution(s) claimed herein would not be functional, beyond speculating that the affinity might not be about 3-fold better than the parent antibody (and, as noted above, the claims other than claim 114 do not require this improvement in affinity). Hence, Applicants submit that the presently claimed variable domains and antibodies are enabled by the specification.

Reconsideration and withdrawal of the enablement rejection is respectfully requested in view of the above.

Section 102 - Claims 115-117, 123 and 127

Claims 115-117, 123 and 127 are rejected under 35 USC Section 102(e) or 102(b) as anticipated by US Patent No. 5,530,101 (hereinafter "the '101 patent") or Queen *et al. PNAS (USA)* 86:10029-10033 (1989) (hereinafter "Queen *et al.*"). The Examiner contends that the '101 patent and Queen *et al.* teach a humanized anti-Tac antibody wherein amino acid 93 is substituted in the heavy chain, using the aligned Kabat Eu sequence to provide the framework for the humanized antibody.

Applicants point out that - as explained earlier in prosecution - the substituted 93 FR residue in the cited references is not 93H "utilizing the numbering system set forth in Kabat" (see page 13, line 33 through to line 22 on page 14 of the present application) as required by claims 115-117, 123 and 127 of the present application. In particular, as noted on page 6 of the amendment hand carried to the Office on 10/7/97, residue no. 93 in the heavy chain of the anti-Tac antibody in the cited references, is actually 89H utilizing the numbering system set forth in Kabat. The cited references use a sequential numbering system, rather than the Kabat numbering system claimed herein.

Reconsideration of the 102(e) and 102(b) rejections based on the '101

patent and Queen *et al.* is respectfully requested in view of the above.

Section 102 - Claims 43, 44, 48, 55, 67, 71, 105, 115-117, 120 and 127

Claims 43, 44, 48, 55, 67, 71, 105, 115-117, 120 and 127 are rejected under 35 USC Section 102(e) as being anticipated by the '101 patent. The Examiner urges that FR substitutions 38L, 67L, 69H, 73H and 93H are taught by the '101 patent. Specifically, the Examiner contends that amino acids 38 or 67 are substituted in the light chain of the Fd79 and M195 antibodies, respectively, and amino acids 69, 73 or 93 are substituted in the heavy chains of the CMV5, mik-β1 and Fd138-80 antibodies, respectively. The '101 patent is further alleged to teach (in the abstract thereof) that the humanized antibodies therein will be substantially non-immunogenic in humans.

Applicants submit that the presently claimed FR 38L, 67L, 69H and 93H substitutions are different from those in the '101 patent to which the Examiner refers, since the numbering of the presently claimed FR substitutions utilizes the numbering system set forth in Kabat, whereas the '101 patent uses sequential numbering for the residues. In particular, VL residue 38 of Fd79 is a CDR residue, as opposed to a FR residue (note Table 1 in column 43 of the '101 patent which states that residue 38 is in "Category 1" and therefore is a CDR residue; see lines 66-67 in column 13 of the '101 patent); VL residue 67 of M195 is FR residue 63L utilizing the numbering system set forth in Kabat (see page 8 of Applicants' 10/7/97 amendment); VH residue 69 of CMV5 is 68H utilizing the numbering system set forth in Kabat (see page 9 of the 10/7/97 amendment); and VH residue 93 of Fd138-80 is FR residue 89H utilizing the numbering system set forth in Kabat (see page 7 of the 10/7/97 amendment).

As to the FR 73H substitution (utilizing the numbering system set forth in Kabat) claimed herein, Applicants submit that the disclosure of the humanized mik-β1 antibody is too late to qualify as Section 102 prior art to claim 115 which recites that substitution. See page 11, first full paragraph of Applicants' 1/15/99 amendment.

Finally, as to the recitation in claim 105 herein that the humanized antibody "lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient", Applicants have shown that antibodies humanized according to one preferred embodiment of the present invention possess this property. See the Shak Declaration filed 8/24/99. The '101 patent merely states that the humanized antibodies will be "substantially non-immunogenic" in humans, but fails to disclose that the humanized antibodies lack substantial immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient.

Reconsideration and withdrawal of the Section 102(e) rejection is respectfully requested in view of the above.

Section 102(e) - Claim 128

Claim 128 is rejected under 35 USC Section 102(e) as being anticipated by the '101 patent. The Examiner states that the language "up to" 3-fold reads on anything below 3-fold.

Claim 128 pertains to a humanized antibody which binds antigen more tightly than the parent antibody (up to about 3-fold more tightly). The Queen patents state that the humanized antibodies therein bind the target antigen with the same affinity, or bind less tightly, than the parent antibody. See pages 21-22 of Applicants' amendment filed 8/24/98. While humanized M195 was later discovered to bind antigen up to about 3-fold more tightly than the parent antibody bound antigen (see paragraph 2 on page 2 of the 8/30/99 amendment), this property of the humanized M195 antibody is not described in the '101 patent (see lines 28-29 in column 60 of the '101 patent).

Reconsideration and withdrawal of the Section 102(e) rejection of claim 128 is respectfully requested.

Section 102(e) - Claim 113

Claim 113 is rejected under 35 USC Section 102(e) as being anticipated

by US Patent 5,693,762 ("the '762 patent") for the same reasons set forth in paper No. 27 for the rejection of previous claims 22-25, 38 and 39.

The Examiner contends that the '762 patent teaches "as a principle, a framework is used from either a human immunoglobulin which is unusually homologous to the donor immunoglobulin, or a consensus framework from many human antibodies is used".

Applicants submit that this disclosure in the '762 patent simply fails to anticipate the presently claimed "consensus human variable domain" in claim 113 as defined by the present specification. See the discussion of the '762 patent on pages 13-14 of the 8/24/98 amendment. The Examiner states on page 11 of the above Office Action that it 'is only Applicant's interpretation that the term "consensus framework" from '762 patent was not intended to refer to a sequence representing the most frequently occurring amino acids in the present invention'. Applicants respectfully disagree. Indeed the Office initially suggested the alternative interpretation for the term "consensus framework" as it was used by Queen *et al.* See page 4 of the Office Action dated 12/23/96 in which Examiner Nolan stated:

> "Regarding the consensus sequence, the combination of references teach the human framework regions having a significantly high degree of sequence homology (conservative regions). Queen et al. in particular point to Kabat as demonstrating that this was known in the art well in advance of applicant's filing date, see reference 38, cited by Queen et al." (Emphasis added).

The Queen *PNAS* paper to which Examiner Nolan referred, was concerned with using a human framework region from a human immunoglobulin which was unusually homologous to the donor immunoglobulin, and failed to mention a consensus human variable domain as that expression is used in the present application. Hence, the Office has previously used the expression "consensus sequence" to describe the highly homologous approach taught by Queen *et al.*

Nothwithstanding this, Applicants note that in order to anticipate a claimed invention, the reference alone much teach each and every element of the claim. Even if it were the case that the "consensus framework" in the '762 patent was intended to refer to an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins (see page 14, lines 29-31 of the present application), which is denied, the Office has not shown that the '762 patent unambiguously disclosed the selection invention recited in claim 113 herein pertaining to a "consensus human variable domain of a human heavy chain immunoglobulin subgroup". The Office has combined the '762 patent with Kabat *et al.* (see Section 103 discussion below) in an attempt to show that this particular consensus sequence had been disclosed previously. Hence, Applicants submit that claim 113 is novel over the '762 patent. Applicants will demonstrate in the following section how the invention set forth in claim 113 is also nonobvious over the '762 patent, due to the unexpected results attributable thereto.

Reconsideration and withdrawal of the Section 102 rejection based on the '762 patent is respectfully requested in view of the above.

Section 103

Claims 113, 115-118, 123 and 127-128 are rejected under 35 USC Section 103 as being unpatentable over the '762 patent in view of Kabat *et al.*

First, it is noted that the Examiner relies on the rejection based on the '762 patent in view of Kabat *et al.* for the same reasons as set forth in paper no. 27 (Applicants assume paper no. 34 - Examiner Nolan's Office Action dated 12/23/97 is intended). Examiner Nolan previously indicated that the unexpected results would overcome the 103 rejection based on the '762 patent combined with Kabat *et al.* (see Paper no. 37; 8/13/98 Interview Summary).

Applicants rely on the unexpected results attributable to the consensus human variable domain of a human heavy chain immunoglobulin subgroup as demonstrating that the presently claimed antibodies are not obvious over

the '762 patent combined with Kabat *et al.* See pages 18-23 of the 8/24/98 amendment and the Shak declaration attached thereto.

The Examiner urges that "the arguments that the claimed invention is unexpected are not applicable, because the claims are broad, and drawn to any antibodies, and not specifically the claimed antibodies, wherein their specific target antigens, and their binding properties are not disclosed in the claims."

Applicants submit that the Examiner's basis for ignoring the evidence of unexpected results is legally flawed - at least with respect to (1) the lack of significant immunogenicity of the claimed humanized antibodies upon repeated administration to a human patient, *e.g.* to treat a chronic disease in that patient and (2) the ability to make many strong affinity antibodies, thus avoiding tailoring each human framework to each non-human antibody to be humanized. Those unexpected results provide objective evidence of non-obviousness. *Specialty Composites v. Cabot Corp.*, 845 F. 2d 981, 6 USPQ 2d 1601 (Fed. Cir. 1988).

As to unexpected result (1), Applicants have demonstrated that antibodies humanized using a consensus human variable domain of a human heavy chain immunoglobulin subgroup as set forth in claim 113 herein lack significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient. This was shown in the Shak Declaration for humanized anti-HER2, anti-IgE, anti-VEGF and anti-CD11a antibodies. See pages 18-21 of the 8/24/98 amendment and the Shak Declaration attached thereto. Hence, this unexpected property is not linked to certain antibodies or specific target antigens, but is generally applicable and the claims are commensurate in scope with the unexpected result relied upon.

Turning now to unexpected result (2), Applicants have shown that a consensus human variable domain of a human heavy chain immunoglobulin subgroup as set forth in claim 113 can be used to generate many different strong affinity humanized antibodies, including anti-HER2, anti-CD3,

anti-CD18, anti-IgE, anti-CD11a and anti-VEGF humanized antibodies (see pages 22-23 of the 8/24/98 amendment). Again, this further unexpected property is not dependent on the antibody or target antigen, and hence should be considered with respect to the non-obviousness of the presently claimed antibodies.

Hence, Applicants submit that claim 113 directed to a humanized variant comprising a consensus human variable domain of a human heavy chain immunoglobulin subgroup is non-obvious over the cited art, because of unexpected results (1) and (2) noted above.

As to the other rejected claims, Applicants point out that claim 115 recites FR substitutions at one or more of positions 24H, 73H, 76H, 78H and 93H, utilizing the numbering system set forth in Kabat. The Office has not shown how the cited art disclosed or suggested substitution of FR residues 24H, 76H, 78H and 93H, utilizing the numbering system set forth in Kabat; and, as noted above, the disclosure concerning substitution of 73H in the mik-β1 antibody is too late to qualify as Section 102 prior art to the invention set forth in claim 115 herein. With regard to claim 117, the Office fails to teach a humanized antibody with FR substitution(s) limited to positions 24H, 73H, 76H, 78H and 93H, utilizing the numbering system set forth in Kabat. As to claim 118, the Office has not demonstrated how the art would have taught combining the listed FR substitution(s) in claim 115 with a consensus human variable domain. With regard to claim 123, as noted previously, substituted 93 FR residue in Queen's anti-Tac or Fd138-80 antibodies is not the same as FR substitution 93H "utilizing the numbering system set forth in Kabat." Finally, with respect to claim 128, as noted above, the Queen patents state that the humanized antibodies therein bind the target antigen with the same affinity, or bind <u>less tightly</u>, than the parent antibody. See pages 21-22 of Applicants' amendment filed 8/24/98. While humanized M195 was later discovered to bind antigen up to about 3-fold more tightly than the parent antibody bound antigen (see paragraph 2 on page 2 of the 8/30/99 amendment), this property of the humanized M195 antibody is not described in the '101 patent (see lines 28-29 in column 60 of the '101

patent). The ability to bind antigen more tightly than the parent antibody was a further unexpected result observed with respect to certain humanized antibodies of the present application.

Reconsideration and withdrawal of the Section 103 rejection of claims 113, 115-118, 123 and 127-128 is respectfully requested in view of the above.

Respectfully submitted,

GENENTECH, INC.

Date: April 25, 2001

By:
Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 113 and 114 have been amended as follows:

113. (Three Times Amended) A humanized variant of a non-human parent antibody which binds an antigen [with better affinity than the parent antibody] and comprises a consensus human variable domain of a human heavy chain immunoglobulin subgroup wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another [, wherein the humanized variant binds antigen up to about 3-fold more tightly than the parent antibody binds antigen].

114. (Amended) The humanized variant of claim [113] 128 which binds the antigen about 3-fold more tightly than the parent antibody binds antigen.

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: M. Davis **CERTIFICATE OF MAILING** I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on April 25, 2001 Wendy M. Lee

PETITION AND FEE FOR THREE MONTH EXTENSION OF TIME
(37 CFR 1.136(a))

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicants petition the Commissioner of Patents and Trademarks to extend the time for response to the Office Action dated October 25, 2000 for three months from January 25, 2001 to April 25, 2001. The extended time for response does not exceed the statutory period.

Please charge Deposit Account No. 07-0630 in the amount of $890.00 to cover the cost of the extension. Any deficiency or overpayment should be charged or credited to this deposit account. A duplicate of this sheet is enclosed.

Respectfully submitted,
GENENTECH, INC.

Date: April 25, 2001

By: _____
Wendy M. Lee
Reg. No. 40,378
Telephone No. (650) 225-1994

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09157
PATENT TRADEMARK OFFICE

Interview Summary

Application No.	Applicant(s)
08/146,206	Carter et al
Examiner	**Group Art Unit**
Minh-Tam Davis	1642

All participants (applicant, applicant's representative, PTO personnel):

(1) *Minh-Tam Davis* (3) _____

(2) *Ewndy Lee* (4) _____

Date of Interview *Apr 26, 2001*

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy is given to 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No. If yes, brief description:

_____

_____

Claim(s) discussed: _____

Identification of prior art discussed:

_____

_____

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Applicant requests an iinterview if the case is not ready for allowance following entry of the amendment to be filed today.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i)☒ It is not necessary for applicant to provide a separate record of the substance of the interview (if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

7/13/01

#6
7/13/01

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: M. Davis **Certificate of Facsimile Transmission Under 37 CFR § 1.8** In accordance with CFR § 1.6(d), this correspondence addressed to Examiner Minh-Tam Davis, The Patent and Trademark Office, Washington, DC 20231 is being transmitted to facsimile No. (703) 308-4426 on July 13, 2001 Wendy M. Lee

AMENDMENT TRANSMITTAL

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated as shown below.

	Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra	Rate	Additional Fees
Total	82	-	86	0	18	$0.00
Independent	8	-	9	0	80	$0.00
__ 0Multiple dependent claim(s), if any					270	$0.00
					Total Fee Calculation	$0.00

X
X

No additional fee is required.
The reference O'Connor *et al. Protein Engineering* 11(4):321-328 (1998) is attached.

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 07-0630.

Respectfully submitted,
GENENTECH, INC.

Date: July 13, 2001

By: _____
Wendy M. Lee
Reg. No. 40,378
Telephone No. (650) 225-1994

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PATENT TRADEMARK OFFICE

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Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE 7/13/01

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: M. Davis Certificate of Facsimile Transmission Under 37 CFR § 1.8 In accordance with CFR § 1.6(d), this correspondence addressed to Examiner Minh-Tam Davis, The Patent and Trademark Office, Washington, DC 20231 is being transmitted to facsimile No. (703) 308-4426 on July 13, 2001 Wendy M. Lee

SUPPLEMENTAL AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

IN THE CLAIMS:

Please amend claims 113 and 128 as indicated below:

64 113. (Three times amended) A humanized variant of a non-human parent antibody which binds an antigen and comprises a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another.

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128. (Twice Amended) A humanized variant of a non-human parent antibody which binds an antigen, wherein the humanized variant comprises Complementarity Determining Region (CDR) amino acid residues of the non-human parent antibody incorporated into a human antibody variable domain, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another, and wherein the humanized variant binds the antigen more tightly than and up to about 3-fold more tightly than the parent antibody binds antigen.

Please add the following claims:

--129. A humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution where the substituted FR residue:

(a) noncovalently binds antigen directly;

(b) interacts with a CDR; or

(c) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another, and wherein the substituted FR residue is at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 24H, 36H, 39H, 43H, 45H, 69H, 70H, 73H, 74H, 76H, 78H, 92H and 93H, utilizing the numbering system set forth in Kabat.

130. The humanized variable domain of claim 129 wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained.

131. The humanized variable domain of claim 129 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.--

REMARKS

Applicants wish to thank Examiners Davis and Caputa for granting an interview to the representatives of Applicants on July 3, 2001. It is noted that the interview was terminated before its completion due to a fire alarm and evacuation of the building. The response herein reflects points raised by the Office during the interview. To the extent that issues remain in the case following entry of this and the previous amendment, Applicants respectfully request a further interview given the protracted prosecution of the case as discussed in the interview.

The pending claims

In the above-noted interview Examiner Caputa asked how the framework in claim 113 differed from the "consensus framework from many human antibodies" as in column 13 of the cited Queen '762 patent. In the interests of expediting prosecution, Applicants have amended claim 113 herein to recite the language found on page 14, lines 29-31 of the present application. The differences between the disclosure of the '762 patent and the invention set forth in claim 113 will be discussed below.

As discussed in the interview, claim 128 is amended herein to emphasize that the humanized antibody of this claim is one with better affinity than the non-human parent. This amendment obviates the §102 rejection over the disclosure of the '101 patent.

Claims 129-131 have been added herein. Claim 129 represents a combination of claims 43 and 115 and includes the FR substitution language from claim 128. Claims 130-131 employ language from claims 44 and 45, respectively.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**" Applicants submit that the amendments do not introduce new matter and therefore should be entered. Following entry of this amendment, claims 43-105 and 113-131 will be pending in the present application.

As was pointed out in the interview, the present application contains three different types of independent claims: (1) claims 43, 72, 104, 105 and 115 encompassing humanized antibody variable domains or antibodies comprising FR substitution(s) including one or more FR substitutions from a specified selection of FR positions; (2) claim 128 directed to a humanized variant which binds the antigen more tightly than the parent antibody binds antigen (up to about 3-fold more tightly); and (3) claim 113 directed to a humanized antibody comprising non-human CDR and FR residue(s) incorporated into a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup.

Section 102

A comprehensive reply to the outstanding Section 102 rejections can be found in the amendment dated April 25, 2001. As discussed in the interview, it is believed that the Section 102 rejections should be withdrawn.

With respect to claims 43, 72, 104, 105 and 115, Applicants pointed out that Queen used sequential numbering, rather than Kabat numbering, for the FR residues, such that the 93H, 38H, 67L and 69H FR substitutions according to Kabat herein were not disclosed by Queen. As to the 73H FR substitution claimed herein, Applicants will submit shortly a swearing behind declaration showing completion of the invention of a humanized variable domain or antibody comprising that FR substitution, prior to cited Queen patent.

As to claim 128, Applicants pointed out that Queen did not describe humanized antibodies with improved affinity - affinity was either about the same or worse than the rodent antibody. The amendment herein clarifies that claim 128 pertains to antibodies with better affinity than the non-human parent antibody.

Finally, Applicants submit that recitation of "a human variable domain comprising the most frequently occurring amino acid residues at each

location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup" in claim 113 renders the humanized antibody therein novel over the cited Queen '762 patent. The Section 103 rejection will be addressed below.

Withdrawal of the outstanding Section 102 rejections is respectfully requested.

Section 112, first paragraph, scope

A full and complete response to the outstanding rejection of claims 43-105 and 113-128 may be found in the communication to the Office dated April 25, 2001.

In the outstanding Office Action, the Examiner maintains that each of the claims presented is not enabled by the disclosure. The basis for the assertion of the Examiner is that she believes the practice of the invention as reflected in each of the claims presented would constitute undue experimentation. Based on the points raised by the Examiner in the July 3 interview and the outstanding Office Action, Applicants believe this conclusion is based on misunderstandings of the law governing enablement, particularly as it pertains to the issue of undue experimentation, and a mischaracterization of the claims at issue and the disclosure. Moreover, Applicants will summarize hereinbelow relevant evidence which demonstrates the reproducibility of the methods disclosed in the present application for generating useful humanized antibody variable domains and antibodies encompassed by the claims herein.

Enablement must be measured in relation to the claims, the disclosure and what is known to a person skilled in the art. See, *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). Undue experimentation, in turn, is a conclusion based on a number of discrete factual determinations. *In re Wands*, 858

F.2d 731, 737 (wherein the court listed eight factors that must be considered as a group when determining an issue of undue experimentation). In the present rejection, the only factors that apparently have been considered by the Examiner are the breadth of the claims and unpredictability in the art.

With respect to the scope of the claims, it is respectfully submitted that the Examiner has not accurately construed the claim scope, either in the rejections set forth in the outstanding Office Action or as characterized during the interview of July 3.

First, as has been noted in previous communications, only one claim (claim 114) specifically requires a three-fold increase in affinity of the humanized antibody relative to the non-human parent antibody. Claim 128, as amended, requires a binding affinity greater than the parent antibody, up to about three times the parent antibody affinity. Claims 43 to 105, 113 and 115 to 127 each contain no reference to minimum binding affinity relative to the parent antibody. Assertions that it would not have been possible to produce a humanized antibody subject to these claims having a three-fold increase in binding affinity are simply irrelevant to all but one claim.

Second, a requirement in each claim presented is that the variable domain retain the functional capacity to bind the antigen bound by the parent antibody. Thus, claims are not directed to single amino acid substitutions in an abstract sense that result in polypeptides that are inoperative as antibody binding domains. Instead, each of the claims presented requires the resulting humanized antibody variable domain or antibody to retain the antibody binding specificity of the parent antibody, and certain of the claims require the binding affinity to be greater than the parent antibody. Omitting the antibody binding limitation present in each claim improperly changes the scope of the claim.

Third, each of the independent claims is further limited in respect of one or more specific and objectively defined physical attributes of the resulting humanized antibody variable domain or antibody. For example, claim 43 identifies -- and thereby limits the claimed invention to -- a finite number of species of antibody binding domains which comprise amino acid substitutions in said binding domain selected from a finite range of substitutions in the framework region. If this physical characteristic of the humanized antibody variable domain is not present, it is outside the scope of this claim. Similarly, the claims do not encompass alterations of a human antibody variable domain that do not result in antibodies that bind to the antigen bound by the parent antibody.

Thus, it is respectfully submitted that the specific physical and functional characteristics of the claimed antibody variable regions must be given weight in determining the scope of the claims. The failure of the Examiner to do so has resulted in an improper characterization of the claimed invention, which is fundamental to the determination of enablement.

The second issue upon which the Examiner has not given sufficient weight are the extensive teachings in the disclosure, in view of what was known in the art as of the time of filing of the present application. The present disclosure provides more than ample direction to a person skilled in the art to rely upon in producing the variable domains and antibodies falling within the scope of the present claims. In particular, the present disclosure provides specific guidance to a person skilled in the art to produce, alter and select variants falling within the scope of the claims without the exercise of undue experimentation.

For example, the disclosure at pages 10-16, 20-29 and in the working examples recites a summary of the process to be used to produce the claimed humanized antibody domains and antibodies. As noted therein, steps for identifying and producing the variant sequences are described,

as are a variety of physical attributes of the resulting variants that are to be selected for through the process described therein (*e.g.*, the substituted FR residue interacts with a CDR, non-covalently binds antigen directly or participates in the V_L-V_H interface). A person reasonably skilled in this field would face no difficulty in taking any parent antibody having a particular binding specificity and, following the explicit and comprehensive teachings of the present disclosure, construct and select humanized antibody domains and antibodies as defined in the claims.

The third basis of the Examiner's rejection appears to be the belief that the claims cannot be practiced without undue experimentation. Undue experimentation is a conclusion that must be reached after considering a number of discrete factors. Two of these, claim scope and the teachings of the disclosure, have been addressed above and in the earlier response to the outstanding Office Action. In addition, the Examiner appears have relied on an assumption that there is an abnormally high level of unpredictability in the field of the invention. In particular, the Examiner is apparently asserting that there is such an inherent degree of unpredictability in the art that no claim to a humanized antibody could ever issue if it were not limited to a specifically defined amino acid sequence associated with a specific antibody specificity. This is an inaccurate characterization of the level of unpredictability in the field of the invention at the time the present application was filed, and is used in an improper manner by the Examiner in light of law governing lack of enablement due to undue experimentation.

Unpredictability in the art, standing alone, is not a conclusion that can support a rejection on the basis of lack of enablement. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Instead, it is a factor whose significance must be assessed in making the legal determination of whether practice of the claimed invention would involve undue experimentation. Moreover, the fact that an art has unpredictability

associated with it does not condemn any claim that goes beyond a specific working example. As §2164.03 of the MPEP provides:

> The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art.

In the present case, neither the Examiner's characterization of unpredictability nor the assessment of the significance of unpredictability in light of the present disclosure is accurate.

As to the former issue, and as noted in the earlier response to the outstanding Office Action, the number of examples of successful modifications (*i.e.*, modifications resulting in functional humanized antibody binding domains) made according to the teachings of the present disclosure far exceeds the number suggested by the Examiner. For example, for one target antigen (HER2), eight successful variants were constructed using the procedures of the present invention. Each of these variants preserved binding affinity of a nature to make it a useful humanized binding domain.

Examiner Davis explained in the interview her opinion that variants (*e.g.* huMAb4D5-2 and huMAb4D5-3) without all 5 FR substitutions of the huMAb4D5-8 variant were not able to bind antigen with appropriate affinity.

With respect to the huMAb4D5-2 variant in Table 3, it was acknowledged that the variant with the single FR substitution did not appear to have growth inhibitory activity in the SK-BR-3 assay used. However, the

undersigned explained that even the 4.7nM Kd of this variant rendered it useful, *e.g.*, for diagnostic uses (see pages 55-57), as an immunotoxin (see pages 58-59), and/or for killing cells *in vivo* via Antibody Dependent Cellular Cytotoxicity (ADCC, see pages 59-60). Indeed, the affinity of the huMAb4D5-2 variant significantly surpasses the affinity of the murine and humanized anti-gD antibodies in column 45 of the cited Queen '762 patent, for instance. There is nothing in the art to indicate that 4.7nM is not a useful Kd. The other variant relied on by the Examiner as supporting her view that the claims were not enabled (huMAb4D5-3 in Table 3 with 4.4nM Kd) would also have the above-noted uses in addition to its ability to inhibit the proliferation of breast cancer cells as assessed by the SK-BR-3 assay. Hence, it was emphasized that the antibodies of the present invention need not have superior binding affinities in order to be useful.

Examiner Caputa asked what evidence was available to demonstrate that the teachings of the present application could be applied to other useful humanized antibodies.

Applicants are able to demonstrate that humanized antibody variants that bind at least seven distinct antigens have been made based on the teachings in the above patent application. For each antigen, several humanized antibody variants with the claimed FR substitution(s) could be made. In particular:

1. Example 1 on pages 63-74 describes several humanized variants which bound HER2 comprising the presently claimed FR substitution(s). Each of those variants was able to bind HER2 antigen (see Table 3 on page 72).

2. Example 3 on pages 79-88 describes eight humanized anti-CD3 antibody variants ($BsF(ab')_2v1$ as well as variants v6-12) which comprised the presently claimed FR substitutions. That example describes the $BsF(ab')_2v1$ variant (see huxCD3v1 in Fig. 5) and the other variants which were useful for retargeting the cytotoxic activity of human CD3+

CTL against HER2 overexpressing breast cancer cells (see, page 79, first paragraph, and Shalaby *et al. J. Exp. Med.* 175:217-225 (1992), of record). The FR substitutions in the BsF(ab')$_2$v1 variant (71L, 71H, 73H and 78H) were those which (a) non-covalently bound antigen directly; (b) interacted with a CDR; or (c) participated in the V_L-V_H interface, such FR substitutions being described and enabled by the present specification. Example 3 describes how the affinity of the humanized antibody BsF(ab')$_2$v1 was further improved by incorporating additional rodent CDR amino acid residues in the humanized antibody to generate BsF(ab')$_2$v9. In addition, that example describes variants with further FR substitutions at positions 75H and/or 76H.

3. Example 4 on page 89 describes yet a further example of the presently claimed humanized antibody variable domains/antibodies. The humanized anti-CD18 antibody included the presently claimed FR substitutions that (a) non-covalently bound antigen directly; (b) interacted with a CDR; or (c) participated in the V_L-V_H interface, and were identified using molecular modeling as taught in the present application.

4. Presta *et al. Cancer Research* 57:4593-4599 (1997) (of record) describes nine humanized anti-VEGF variants that were generated following the enabling disclosure of the present application.

5. Various humanized anti-Protein C variants are described in O'Connor *et al. Protein Engineering* 11(4):321-328 (1998) (copy attached), those variants being enabled by the present application.

6. Humanized antibody variants which bind the IgE antigen covered by certain claims herein have also been made (see Presta *et al. J. Immunol.* 151(5): 2623-2632 (1993) (of record)).

7. Werther *et al. J. Immunol.* 157(11): 4986-4995 (1996) (of record) is concerned with the humanization of anti-LFA-1 antibodies and describes several humanized antibody variants encompassed by the present claims.

These facts suggest that the "unpredictability" in the art is in fact much lower than suggested by the Examiner. When this actual level of unpredictability is then considered in view of the claim scope and the breadth of the disclosure, it becomes clear that unpredictability in the present application is not a factor that can support an assertion of undue experimentation. Indeed, through the teachings of the present disclosure, the moderate degree of unpredictability that exists in the art does not operate as a barrier to practice of the claimed invention, particularly in light of the teachings of the disclosure as to how to produce, identify and select variants falling within the scope of the claims.

As a consequence, it is respectfully submitted that the basis of the Examiner's belief that there is a lack of enablement due to undue experimentation is misplaced and should be withdrawn. Moreover, it is respectfully submitted that unless the Examiner can provide specific evidence demonstrating that the procedures disclosed in the present application will not yield success in producing humanized antibody variable domains as claimed, to counter the evidence provided in the specification and the specific responses, the maintenance of this rejection is improper. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971). Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections based on lack of enablement.

Section 103 rejection

Claims 113, 115-118, 123 and 127-128 are rejected under Section 103 as being unpatentable over the Queen '762 patent in view of Kabat *et al.* Applicants responded to the rejection in the amendment dated April 25, 2001 and that response is supplemented hereinbelow.

At the outset, it is noted that the 103 rejection as to 115-118, 123, 127-128 should fall with the withdrawal of the Section 102 rejections of these claims, since the Office has not advanced any reason why one would substitute the presently recited FR residues, or why one would

have thought it would be possible to make a humanized antibody with improved affinity compared to the rodent antibody based on the cited art.

With regard to claim 113, now reciting "a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup", Applicants pointed out that it is believed that a *prima facie* case for obviousness of this invention has not been established; and even if it had, unexpected results provide objective evidence as to the patentability of the presently claimed invention.

Applicants' representatives explained in the interview that the term "consensus framework from many human antibodies" was used in the Queen patent synonymously with "a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized" - the position also taken by a former Patent Examiner (see page 10 of the amendment dated April 25, 2001). This is abundantly clear from a reading of the relied upon reference to a "consensus framework from many human antibodies" in the '762 patent. Immediately after this phrase in column 13, first full paragraph, the '762 patent states "For example, comparison of the sequence of a mouse heavy (or light) chain variable region against human heavy (or light) variable regions in a data bank (for example, the National Biomedical Research Foundation Protein Identification Resource) shows that the extent of homology to different human regions varies greatly, typically from about 40% to about 60-70%. By choosing as the acceptor immunoglobulin one of the human heavy (respectively light) chain variable regions that is most homologous to the heavy (respectively light) chain variable region of the donor immunoglobulin, fewer amino acids will be changed in going from the donor immunoglobulin to the humanized immunoglobulin. Thus, it is clear from the '762 patent that what it intended by the "consensus framework from many human antibodies" was indeed the "most homologous" human framework region as selected in the quoted paragraph of the '762 patent above. Thus, Applicants submit that the rejection based on the

combination of the '762 patent and Kabat *et al.* has been made with the benefit of hindsight of the present invention, which is impermissible.

Aside from the lack of teaching or motivation in the '762 patent to use a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup, the '762 patent teaches away from this approach. Indeed, Queen taught the importance of selecting an unusually homologous human framework in order to avoid distorting the CDRs (column 13, lines 19-27). Applicants have shown previously how antibodies humanized with the human variable domain in claim 113 lack the unusually high homology to the non-human variable domain (paragraph bridging pages 17-18 of the amendment filed August 24, 1998), but nonetheless bind antigen extremely well. For instance, Applicants referenced the humanized anti-CD18 antibody with only 53% homology between the rodent and human framework sequences; humanized anti-IgE antibody with only 58% homology; humanized anti-CD11a with only 57% homology etc. These homologies were much lower that the homologies considered by Queen to be critical to avoid distorting the CDRs and for retaining affinity. The present application goes beyond the Queen method and discloses the benefits of using a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup for humanizing many different antibodies. This was not possible based on Queen's work which required that the human variable domain be tailored to each new rodent variable domain sequence to be humanized.

Applicants believe that the above arguments make out a strong case for patentability of the presently claimed invention over the cited combination of the '762 patent and Kabat *et al.* Moreover, Applicants are able to demonstrate that the presently claimed invention is patentable over the cited art due to the unexpected results attributable thereto. In particular, Applicants have demonstrated through the Shak declaration that antibodies directed against four different antigens humanized with

the presently claimed human variable domain in claim 113 display the unexpected property of lack of significant immunogenicity upon repeated administration to a human patient. This was not predictable in view of art such as Isaacs *et al. The Lancet* 340:748-752 (1992) (of record) in which 3/4 patients developed inhibitory antiglobulins upon repeated administration of the prior art humanized antibody thereto.

The Examiner had indicated that the unexpected results are not applicable because "the claims are broad, and drawn to any antibodies, and not specifically the claimed antibodies, wherein their specific target antigens, and their binding properties are not disclosed in the claims". Applicants submit that the Shak declaration filed demonstrates that the unexpected result applies regardless of the antigen or binding properties of the antibodies; the unexpected result was shown for humanized anti-HER2, anti-IgE, anti-CD11a and anti-VEGF antibodies. Hence, Applicants submit that the unexpected results are commensurate in scope with the invention recited in claim 113.

Thus, Applicants submit that the presently claimed invention is patentable over the cited art.

Applicants believe that this application is now in order for allowance and look forward to early notification to that effect.

Respectfully submitted,

GENENTECH, INC.

Date: July 13, 2001

By: _____

Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994

Part / #61
7/13/01

Serial No.: 08/146,206

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:
Please amend claims 113 and 128 as follows:

113. (Three times amended) A humanized variant of a non-human parent antibody which binds an antigen and comprises a [consensus] human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another.

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128. (Twice Amended) A humanized variant of a non-human parent antibody which binds an antigen, wherein the humanized variant comprises Complementarity Determining Region (CDR) amino acid residues of the non-human parent antibody incorporated into a human antibody variable domain, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another, and wherein the humanized variant binds the antigen more tightly than and up to about 3-fold more tightly than the parent antibody binds antigen.

Please add the following claims:

129. A humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution where the substituted FR residue:
(a) noncovalently binds antigen directly;
(b) interacts with a CDR; or
(c) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another, and wherein the substituted FR residue is at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 24H, 36H, 39H, 43H, 45H, 69H, 70H, 73H, 74H, 76H, 78H, 92H and 93H, utilizing the numbering system set forth in Kabat.

130. The humanized variable domain of claim 129 wherein the substituted residue is the residue found at the corresponding

C

location of the non-human antibody from which the non-human CDR amino acid residues are obtained.

131. The humanized variable domain of claim 129 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

1 DNA WAY
South San Francisco, CA 94080
(650) 225-1994
Facsimile: **(650) 952-9881**

#62

FACSIMILE TRANSMITTAL

DATE: July 30, 2001

Please deliver the following Amendment to:

NAME: Examiner Minh-Tam Davis
U.S. Patent and Trademark office
Washington, DC 20231

Fax No.:(703) 308-4426

FROM: Wendy M. Lee
Registration No.: 40,378

RE: U.S. Serial No.: 08/146,206
Our Docket No.: P0709P1

Number of Pages including this cover sheet - 13

Certificate of Facsimile Transmission Under 37 CFR § 1.8

In accordance with CFR § 1.6(d), this Amendment and Zenapax product information is addressed to Examiner Minh-Tam Davis, The Patent and Trademark Office, Washington, DC 20231 and is being transmitted to facsimile No. (703) 308-4426.

If you do not receive all pages, please notify Wendy Lee at (650) 225-1994.

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: Minh-Tam Davis

Certificate of Facsimile Transmission Under 37 CFR § 1.8

In accordance with CFR § 1.6(d), this correspondence addressed to Examiner Minh-Tam Davis, The Patent and Trademark Office, Washington, DC 20231 is being transmitted to facsimile No. (703) 308-4426 on

July 30, 2001

Wendy M. Lee

SUPPLEMENTAL AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

IN THE CLAIMS:

Please amend claim 128 as follows:

128. (Three Times Amended) A humanized variant of a non-human parent antibody which binds an antigen, wherein the humanized variant comprises Complementarity Determining Region (CDR) amino acid residues of the non-human parent antibody incorporated into a human antibody variable domain, and further comprises Framework Region (FR) substitutions at heavy chain positions 71H, 73H, 78H and 93H, utilizing the numbering system set forth in Kabat.

REMARKS

Applicants confirm having discussed the above application with Examiner Davis in the telephonic interview of July 25, 2001. In that interview, Examiner Davis indicated that on reconsideration the Section 112, first paragraph rejection would be withdrawn except with respect to claim 128. The Examiner considers the claim to antibodies with improved affinity to be enabled only for variants with FR substitutions at all the positions

for the exemplified better-binding variants. Applicants strongly disagree with the rejection of claim 128 for all the reasons previously elaborated. Nonetheless, in order to expedite allowance of the case, claim 128 is amended herein to recite the FR substitutions in the heavy chain variable region of the huMAb4D5-8 and huMAb4D5-6 variants which bound antigen more tightly than the parent antibody. Support for the claim language can be found on page 72, for instance. Due to the recitation of the FR substitutions, the functional language concerning the improved binding has been removed from the claim. The Examiner indicated that such an amendment would address the maintained Section 112 rejection.

The Examiner further stated in the above interview that the previous Section 103 rejection of claims 113, 115-118, 123 and 127-128 would be maintained unless Applicants could demonstrate the unexpected results through a side-by-side comparison of the antibody described in the cited Queen prior art and the antibodies of the present application. Applicants are now able to provide that comparison. In particular, Applicants attach the Physicians' Desk Reference ® (PDR) entry for the humanized anti-Tac antibody (ZENAPAX®) of the Queen prior art. Applicants note that the other humanized antibodies added to the Queen patents by way of CIP applications are not prior art to Applicants' invention set forth in the rejected claims herein.

As noted in section entitled "PRECAUTIONS" in the PDR entry for ZENAPAX®, when patients received multiple doses of that humanized antibody, anti-idiotype antibodies to ZENAPAX® were detected in patients with an overall incidence of 8.4%. The presently disclosed antibodies produce unexpectedly lower immunogenicity compared to that of the Queen antibody. This is demonstrated in the Shak declaration previously submitted which explained that patients receiving multiple doses of the humanized anti-HER2 antibody (HERCEPTIN®) exemplified in the present application only developed an antibody response 0.1% of the time (1 of the 885 patients evaluated; see paragraph 4 of the Shak declaration); and 0% of the patients treated with an anti-IgE antibody humanized according to the

teachings of the above patent specification developed a HAHA response (paragraph 7 of the Shak declaration). The total lack of an immune response in the patients treated with the humanized anti-IgE antibody is particularly unexpected, given that the allergic rhinitis and asthma patients treated therewith were hyper-sensitive to foreign antigens. Likewise, no significant immunogenicity upon repeated administration was observed for the anti-VEGF and anti-CD11a antibodies humanized according to the teachings in the present application. Paragraphs 8 and 9 of the Shak declaration. Applicants submit that this side-by-side comparison shows that the antibodies of the present application possess unexpected properties with respect to minimal or no immunogenicity upon repeated administration to human patients.

Reconsideration and withdrawal of the Section 103 rejection is respectfully requested in view of the above.

Applicants believe that this case is now in order for allowance and look forward to early notification of same.

Respectfully submitted,
GENENTECH, INC.

Date: July 30, 2001

By:
Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please amend claim 128 as follows:

128. (Three Times Amended) A humanized variant of a non-human parent antibody which binds an antigen, wherein the humanized variant comprises Complementarity Determining Region (CDR) amino acid residues of the non-human parent antibody incorporated into a human antibody variable domain, and further comprises [a] Framework Region (FR) substitutions at heavy chain positions 71H, 73H, 78H and 93H, utilizing the numbering system set forth in Kabat [where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another, and wherein the humanized variant binds the antigen more tightly than and up to about 3-fold more tightly than the parent antibody binds antigen].

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/146,206			

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 8/29/01

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) Minh-Tam Davis (3) Wendy Lee

(2) Anthony Caputa (4)

Date of Interview 08/29/01

Type: ☐ Telephonic ☐ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No If yes, brief description:

Agreement ☐ was reached. ☐ was not reached.

Claim(s) discussed:

Identification of prior art discussed:

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicant representative discusses prior art of record & pending claims

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

FORM **PTOL-413** (REV.1-96)

A complete written statement as to the substance of any face-to-face or telephone interview with regard to an application must be made of record in the application, whether or not an agreement with the examiner was reached at the interview.

§1.133 Interviews

* * * * *

(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for response to Office action as specified in §§ 1.111,1.135. (35 U.S.C.132)

§ 1.2. Business to be transacted in writing. All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf Interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below.

The Interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and listed on the "Contents" list on the file wrapper. The docket and serial register cards need not be updated to reflect interviews. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the telephonic interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Serial Number of the application
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (personal or telephonic)
- Name of participant(s)) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desireable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check a box at the bottom of the Form informing the applicant that he need not supplement the Form by submitting a separate record of the substance of the interview.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview:

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner,
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter or the remainder of any period for response, whichever is longer, to complete the response and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the statement attributed to him. If the record is complete and accurate, the examiner should place the indication "Interview record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: Minh-Tam Davis CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on August 30, 2001 Anna Kan Anna Kan

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicants submit herewith patents, publications or other information (attached hereto and listed on the attached revised Form PTO-1449) of which they are aware, which they believe may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 CFR §1.56.

This Information Disclosure Statement is filed in accordance with the provisions of:

[] **37 CFR §1.97(b)**

- within three months of the filing date of the application other than a continued prosecution application under 37 CFR §1.53(d); **or**
- within three months of the date of entry of the national stage of a PCT application as set forth in 37 CFR§1.491, **or**
- before the mailing of the first Office action on the merits; **or**
- before the mailing of the first Office action after the filing of a request for a continued examination under 37 CFR §1.114.

[X] **37 CFR §1.97(c)**

- by the applicant after the period specified in 37 CFR §1.97(b), but prior to the mailing date of any of a final action under 37 CFR §1.113, or a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application, and is accompanied by either the fee set forth in 37 CFR §1.17(p) **or** a statement as specified in 37 CFR §1.97(e), as checked below.

[] **37 CFR §1.97(d)**

- after the period specified in CFR §1.97(c), and is accompanied by the fee set

forth in 37 CFR §1.17(p) **and** a statement as specified in 37 CFR §1.97(e), as checked below.

[If either of boxes 37 CFR §1.97(c) or 37 CFR §1.97(d) is checked above, the following statement under 37 CFR §1.97(e) may need to be completed.]

[] **37 CFR §1.97(e)**Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.

[] **37 CFR §1.704(d)** Each item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application and the communication was not received by any individual designated in §1.56(c) more than thirty days prior to the filing of this information disclosure statement. Therefore, in accordance with the provisions of 37 CFR §1.704(d), the filing of this information disclosure statement will not be considered a failure to engage in reasonable efforts to conclude prosecution under 37 CFR §1.704.

[X] The U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $180.00 to cover the cost of this Information Disclosure Statement under 37 CFR §1.17(p). Any deficiency or overpayment should be charged or credited to this deposit account.

A list of the patent(s) or publication(s) is set forth on the attached revised Form PTO-1449 (Modified).

A copy of the items on PTO-1449 is supplied herewith.

Those patent(s) or publication(s) which are marked with an asterisk (*) in the attached PTO-1449 form are not supplied because they were previously cited by or submitted to the Office in a prior application Serial No. 07/715,272, filed 14 June 1991 and relied upon in this application for an earlier filing date under 35 USC §120.

A concise explanation of relevance of the items listed on PTO-1449 is:

[X] not given

[] given for each listed item

[] given for only non-English language listed item(s) [Required]

[] in the form of an English language copy of a Search Report from a foreign patent office, issued in a counterpart application, which refers to the relevant portions of the references.

In accordance with 37 CFR §1.97(g), the filing of this information disclosure statement shall not be construed as a representation that a search has been made.

In accordance with 37 CFR §1.97(h), the filing of this information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in 37 CFR § 1.56(b).

In the event that the Office determines a fee to be due where none is specifically authorized in this paper, the U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $180.00 to cover the cost of this Information Disclosure Statement under 37 CFR §1.17(p).

Respectfully submitted,

GENENTECH, INC.

Date: August 30, 2001

By: _____

By: Steven X. Cui Reg. No.. 44,637
for Wendy M. Lee Reg. No. 40,378
Telephone No. (650) 225-1994

09157

PATENT TRADEMARK OFFICE

9/4/01

File History Report

□ **Paper number(s) _____ is/are missing from the United States Patent and Trademark Office's original copy of the file history.**

☒ **The following page(s) 1 of paper number 64 is/are missing from the United States Patent and Trademark Office's original copy of the file history.**

□ **The following checked item(s) of paper number _____ is/are missing from the United States Patent and Trademark Office's original copy of the file history.**

□ **PTO-892 Form** □ **PTO-1449 Form**

□ **PTO-948 Form** □ **Other _____**

to this declaration which represent excerpts from our laboratory notebooks with dates obscured.

4. Exhibit A provides the amino acid sequences of humanized 4D5 (anti-HER2) antibody variable domain sequences. A humanized antibody (Hu4D5 Fab) comprising the Hum4D5a V_L and Hum4D5a V_H sequences from Exhibit A (the variable domain sequences of the variant called "huMAb4D5-5" in the above application) was recombinantly produced and found to bind the HER2 antigen as evidenced by the laboratory notebook entries in Exhibit B attached hereto. Hu4D5 Fab comprised a heavy chain variable domain comprising non-human CDR amino acid residues which bound antigen incorporated into a human antibody variable domain, and further comprised a FR amino acid substitution at site 73H. The experimental work in Exhibits A and B was completed prior to September 28, 1990.

We declare further that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: _____

_____
Paul J. Carter

Date: Sept. 4, 2001

Leonard G. Presta
Leonard G. Presta

#63

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

1 DNA WAY
South San Francisco, CA 94080
(650) 225-1994
Facsimile: **(650) 952-9881**

FACSIMILE TRANSMITTAL

DATE: October 2, 2001

Please deliver the following Supplemental Amendment, Vincenti et al. reference, and Declaration under 37 CFR §1.131 with attached Exhibits A and B to:

NAME: Examiner Minh-Tam Davis - Group 1642
U.S. Patent and Trademark office
Washington, DC 20231

Fax No.: (703) 308-4426

FROM: Wendy M. Lee
Registration No.: 40,378

RE: U.S. Serial No.: 08/146,206
Our Docket No.: P0709P1

Number of Pages including this cover sheet - 20

Certificate of Facsimile Transmission Under 37 CFR § 1.8

In accordance with CFR § 1.6(d), this correspondence addressed to The Patent and Trademark Office, Box: Assignments, Washington, DC 20231 is being transmitted to facsimile No. (703) 308-4426

If you do not receive all pages, please notify Wendy Lee at (650) 225-1994.

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: Minh-Tam Davis Certificate of Facsimile Transmission Under 37 CFR § 1.8 In accordance with CFR § 1.8(d), this correspondence addressed to Examiner Minh-Tam Davis at the Patent and Trademark Office, Washington, DC 20231 is being transmitted to facsimile No. (703) 308-4426 October 2, 2001 Wendy M. Lee

#63

10-10-01

SUPPLEMENTAL SUBMISSION

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Original Davis 10/04/01

The undersigned confirms having discussed the present application with Examiners Caputa and Davis in the interview on August 29, 2001. Based on and responsive to that discussion, Applicants wish to provide the following additional observations and information.

Status of Previous Rejections

During the most recent interviews, Examiner Davis indicated that the Section 112 and 102 rejections would likely be withdrawn, but that certain of the claims may continue to be rejected under Section 103. The following comments address the 103 rejection.

Additional Information on ZENAPAX®

Examiner Caputa requested that evidence be presented to demonstrate that ZENAPAX® - for which Applicants provided the side-by-side comparison in the July 30, 2001 amendment - was the same as the antibody in the cited Queen references. To confirm that ZENAPAX® (Daclizumab) is the humanized anti-IL2 receptor antibody described in the cited Queen patents and Queen, *PNAS* (1989) paper, Applicants direct the Examiner's attention to the attached copy of Vincenti *et al. N. Engl. J. Med.* 338:161-165 (1998). Vincenti *et al.* refers to Daclizumab (the generic

name for the ZENAPAX® antibody - see PDR entry attached to the July 30, 2001 amendment) and states in column 2 on page 161 that it is a molecularly engineered human IgG1 incorporating the antigen-binding regions of the parent, murine monoclonal antibody. There, Vincenti cross-references the Queen *et al. PNAS* (1989) paper (ref. no. 14 in Vincenti *et al.*) as describing Daclizumab. Hence, Applicants submit that ZENAPAX®/Daclizumab is the humanized anti-IL2 receptor antibody described in the cited Queen references.

Rejection of Claim 113 under 35 USC 103 based on Queen in view of Kabat

The Office Action dated October 25, 2000 (hereinafter, "Action") includes a rejection of claims 113, 115-118, 123, and 127-128 made under 35 USC 103 as being obvious over Queen in view of Kabat. Applicants submit this response to supplement and clarify their previous remarks.

Applicants have previously explained why the Action's conclusions of obviousness made against claim 113 are formed through improper use of hindsight in interpreting the words of the disclosure of Queen. Applicants have also pointed out functional attributes of the humanized antibodies of claim 113 of the present invention that reflect unexpected results, thus providing a distinct and separate basis for overcoming the rejection imposed under §103. Through this supplemental amendment, Applicants respond to points made by Examiner in the Action, and as suggested in personal and telephonic interviews conducted earlier this year. On the basis of each of these points, Applicants respectfully submit that the Examiner has not presented and cannot sustain a *prima facie* showing of obviousness of the claimed inventions. In particular, the Queen disclosure fails to disclose the requisite motivation to combine it with Kabat to set forth a *prima facie* case of obviousness of claim 113.

It is well established that in order for a combination of references to render an invention obvious, there must be a clear motivation in the references that their teachings can be combined. *In re Avery*, 518 F.2d 1228 (1975, CCPA). The mere fact that references address issues within the same field of the invention does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *ACS Hospital Systems Inc. v. Montefiore Hospital*, 732 F.2d 1572 (Fed. Cir. 1984). In fact, "[t]he references, viewed by themselves and not in retrospect must suggest doing what applicant has done" *In re Skoll*, 523 F.2d 1392 (1975 CCPA). Furthermore, the Federal Circuit and the PTO have made it clear that where a modification must be made to the

prior art to reject or invalidate a claim under 35 USC §103, there must be a showing of proper motivation to do so. In order to establish obviousness, there must be suggestion or motivation in the references. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984).

The Action asserts that combining the references to provide the advantages of the present invention would be obvious. However, it identifies nothing within the applied references that would suggest combining those references to arrive at the claimed invention. Rather, the Action improperly cites the findings of *In re Kerkhoven*, 626 F.2d 846 (C.C.P.A. 1980) to support the conclusion of obviousness. Specifically, the Action states that combining the references "would have logically flowed from their having been individually taught in the prior art, and because patent '762 teaches the use of 'consensus sequence', for the same purpose of producing humanized monoclonal antibodies for therapeutic purposes." Applicants contend, however, that the use of *Kerkhoven* in the present case to support a finding of obviousness is improper as the facts of that case are distinguishable from those at hand.

In *Kerkhoven*, the Appellant's claimed a process for producing a detergent containing a mixture of anionic and nonionic detergent materials. In that method, the Appellant's combined two compositions, <u>each taught by the prior art to be useful for the same purpose</u>, in order to form a third composition that was also useful for the same purpose. The patent examiner rejected the method as obvious in light of the prior art under *35 U.S.C. §103*. The Court of Patent Appeals affirmed the rejection and stated that the idea of combining two compositions taught by the prior art to be useful for the same purpose in order to form a third composition to be used for same purpose as the individual components is *prima facie* obvious. *Id* at 850.

The holding in *Kerkhoven* cannot be applied to the instant situation. Most significantly, the disclosure of Queen does not teach the usefulness of a sequence "comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup" for the purpose of humanizing antibodies, which concept is disclosed and claimed in the present application. In contrast, the Queen patent merely refers to using a "consensus framework from many human antibodies" for humanizing antibodies (column 13, line 7). One of skill in the art interpreting the phrase "many human antibodies" as recited in Queen would construe the phrase to refer to an arbitrarily selected group of human antibodies, with the specification

guiding that such an arbitrarily selected group should consist of sequences that are "unusually homologous to the donor immunoglobulin to be humanized" (column 13, line 6).

There is no specific teaching, suggestion or motivation found in the Queen disclosure that would direct a person of ordinary skill to select sets of consensus sequences that correspond to what is disclosed and claimed in the present application. Specifically, in contrast to Queen, the term "consensus" is used in the present application to refer to the relationship among a well-defined group of human antibody subgroups. See, page 14, lines 29 to 35 and page 15, lines 1-25 of disclosure.

The lack of any specific teaching or motivation in Queen is not cured by the disclosure of Kabat. The Action's analysis of Kabat does not provide any suggestion that the frequency of occurrence of amino acid residues in the immunoglobulin chains can be exploited or used for any particular purpose related to humanizing antibodies.

Indeed, nothing in the '762 patent or in Kabat teaches that a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup is useful for producing humanized monoclonal antibodies for therapeutic purposes. Therefore, regardless of what usefulness may be ascribed to the "consensus framework from many human antibodies" taught in the '762 patent, the sequences taught by Kabat could not have been, and were not, identified in the cited art as being useful for producing humanized monoclonal antibodies for therapeutic purposes. Because the prior art had not equated the potential use of the "consensus framework from many human antibodies" taught in the '762 patent with the potential use of the sequences taught by Kabat, the cited art does not provide motivation to substitute the sequences identified by Kabat for the sequences referred to in the '762 patent.

In summary, in *Kerkhoven*, <u>both</u> components had been taught by the prior art to be useful for the same purpose, and, in addition, the resulting component was also useful for the same purpose. However, in the instant situation only <u>one</u> of the prior art components, namely the "consensus framework from many human antibodies" as recited in the '762 patent, had been referred to for "producing humanized monoclonal antibodies for therapeutic purposes." Therefore, *Kerkhoven* does not control the facts of the present application, and a *prima facie* case of

obviousness on the basis of Queen in view of Kabat is improper because there is no suggestion or motivation to combine the cited references.

Applicants respectfully request that the rejection of claim 113 on the basis of Queen in view of Kabat be withdrawn.

Rejection of Claims 115-118, 123 and 127-128 under 35 USC 103 on the basis of Queen in view of Kabat

Claims 115-118, 123 and 127-128 have also been rejected under 35 USC 103 on the basis of Queen in view of Kabat Since the rationale for this rejection and the facts that control its disposition are distinct from those related to claim 113, Applicants are separately addressing the basis of the rejection of these claims.

Each of the rejected claims recite substitutions at specific FR positions. Applicants have explained that the Queen '762 patent relied on in the Section 103 rejection did not describe a humanized antibody having these specific FR substitution(s), except for antibodies comprising a 73H FR substitution as claimed herein. With respect to the 73H substitution, Applicants provide herewith a swearing behind declaration showing a completion of that invention by the inventors of the present application prior to September 28, 1990 - the 2nd Queen CIP filing date, after which time the disclosure concerning the 73H substitution was added.

The Office has not advanced any reasons why substituting the specifically identified FR positions recited in the claims would have been obvious in view of Queen. The previous 103 rejection was based on the sequential numbering of the FR residues, rather than the Kabat numbering as presently claimed - see the April 25, 2001 amendment which clarifies this distinction at pages 8 and 13. In this regard, Examiner Caputa asked that Applicants emphasize the selection invention claimed herein by contrasting the specifically recited FR substitutions to the disclosure in the Queen patent. Aside from the specific FR substitutions for the exemplified humanized antibodies, Queen refers to FR substitutions in Categories 2-4 (columns 13-15 of the '762 patent). Thus, according to Queen, any one of the approximately 80 V_L FR residues or approximately 87 V_H FR residues can be substituted according to those criteria. This would not provide a specific teaching as to the selection invention set forth in claims herein which recite specific FR positions to be substituted.

In considering the appropriateness of the rejection of these claims on the basis of Queen in view of Kabat, the Examiner's attention is directed to the Federal Circuit decision of *In re Baird*, 16 F.3d 380. In *Baird* the court held that a reference, which discloses a generic formula that encompasses a species claimed by applicant did not render the species obvious because there was no motivation provided to select the particular species that applicant claimed. Moreover, the vast number of species encompassed by the reference's generic disclosure, and the fact that the preferred species of the reference were different from the applicant's species led the court to conclude that the reference did not fairly suggest the selection of the particular species claimed by applicants.

Baird controls the question of non-obviousness of claims 115-118, 123 and 127 in the present situation. As Applicants have previously indicated, the Queen disclosure reveals a genus that encompasses a vast number of species. According to Queen, any one of the approximately 80 V_L FR residues or approximately 87 V_H FR residues can be substituted according to their criteria. This would not provide a specific teaching as to the selection invention set forth in claims herein which recite specifically identified substitutions in FR positions. Further, as explained at the interview, the present case is entitled to a 1991 filing date and, as such, represents one of the early disclosures concerning humanized antibodies. Applicants submit that this should be taken into account when reconsidering the patentability of the present invention over the prior art.

For these reasons, Applicants respectfully request that the rejection of claims 115-118, 123 and 127-128 be withdrawn.

Conclusions

In light of the above and previous amendments and remarks, Applicants respectfully submit that all pending claims as currently presented are in condition for allowance.

Applicants believe that is application is now in condition for allowance, and look forward to early notification that effect. If however, there are outstanding issues, the Examiner is invited to call the undersigned to discuss those.

Respectfully submitted,
GENENTECH, INC.

Date: October 2, 2001

By: _____
Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994

09157
PATENT TRADEMARK OFFICE

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: Method for Making Humanized Antibodies	Group Art Unit: 1642 Examiner: Minh-Tam Davis

DECLARATION UNDER 37 CFR §1.131

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

We, Paul J. Carter and Leonard G. Presta, do hereby declare and say as follows:

1. We are inventors of the subject matter of the above-identified patent application. All work described hereinafter was performed by us or on our behalf in the Unites States of America.

2. Prior to September 28, 1990, we conceived of and reduced to practice a humanized antibody heavy chain variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution at site 73H, utilizing the numbering system set forth in Kabat, as well as an antibody comprising that humanized variable domain.

3. Evidence of the reduction to practice of the claimed invention is set forth in the exhibits attached

to this declaration which represent excerpts from our laboratory notebooks with dates obscured.

4. Exhibit A provides the amino acid sequences of humanized 4D5 (anti-HER2) antibody variable domain sequences. A humanized antibody (Hu4D5 Fab) comprising the Hum4D5a V_L and Hum4D5a V_H sequences from Exhibit A (the variable domain sequences of the variant called "huMAb4D5-5" in the above application) was recombinantly produced and found to bind the HER2 antigen as evidenced by the laboratory notebook entries in Exhibit B attached hereto. Hu4D5 Fab comprised a heavy chain variable domain comprising non-human CDR amino acid residues which bound antigen incorporated into a human antibody variable domain, and further comprised a FR amino acid substitution at site 73H. The experimental work in Exhibits A and B was completed prior to September 28, 1990.

We declare further that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 9/5/01 Paul J. Carter

Paul J. Carter

Date: _____

_____

Leonard G. Presta

Project No._______

Book No._______ TITLE *Humanized 4D5*

From Page No.__

Dennis and Paul,
    here are the human consensus sequences and the proposed
    humanized 4D5 sequences.

```
################################################################################
VARIABLE LIGHT
HuLys has 83% similarity to human kappa subgroup I even when the
CDR sequences are included. The sequences inside the CDR boxes
(Chothia/Lesk definition) can be taken from HuLys or humkapI --
those outside the boxes should be taken from humkapI.

(Kabat/Wu CDR in capital letters; Chothia/Lesk CDR in boxes)

           1                                      10
humkapI   asp ile gln met thr gln ser pro ser ser leu ser ala ser val gly
HuLys

                       20                                 30
humkapI   asp arg val thr ilc thr cys ARG ALA|SER GLN ASP ILE SER SER TYR|
HuLys                                        |    GLY ASN     HIS ASN    |

                                      40
humkapI   LEU ASN trp tyr gln gln lys pro gly lys ala pro lys leu leu ile
HuLys         ALA

              50                                          60
humkapI   tyr|ALA ALA SER|SER LEU GLU SER gly val pro ser arg phe ser gly
HuLys        |TYR THR THR|THR     ALA ASP

                              70                                      80
humkapI   ser gly ser gly thr asp phe thr leu thr ile ser ser leu gln pro
HuLys                                 phc

                                           90
humkapI   glu asp phe ala thr tyr tyr cys GLN GLN|TYR ASN SER LEU PRO TYR|
HuLys             ile                         HIS|PHE TRP     THR     ARG|

                      100
humkapI   THR phe gly gln gly thr lys val glu ile lys arg thr
HuLys
################################################################################
VARIABLE HEAVY
The sequences inside the CDR boxes (Chothia/Lesk definition) can be taken
from KOL or humIII -- those outside the boxes should be taken from humIII.

(Kabat/Wu CDR in capital letters; Chothia/Lesk CDR between bars)

           1                                      10
humiii    glu val gln leu val glu ser gly gly gly leu val gln pro gly gly
kol                           gln                     val             arg

                       20                                     30
humiii    ser leu arg leu ser cys ala ala ser|GLY PHE THR PHE SER ASP TYR
kol                               ser ser    |        ILE         SER

                                      40
humiii    ALA MET|SER trp val arg gln ala pro gly lys gly leu glu trp val
kol              |TYR

               50      52|52a  53         |                60
humiii    ala VAL ILE SER|GLU ASN GLY SER|ASP THR TYR TYR ALA ASP SER VAL
kol           ILE     TRP|ASP ASP        |    GLN HIS
```

To Page No. 23

Witnessed & Understood by me,	Date	Invented by	Date
		Recorded by *Leonard Presta*	EXHIBIT A

From Page No. 22

```
                                                    70
humiii  LYS GLY arg phe thr ile ser arg asp asp ser lys asn thr leu tyr
kol                                                 asn                 phe

         60      62 82a 82b 82c  83                                  90
humiii  leu gln met asn ser leu arg ala glu asp thr ala val tyr tyr cys
kol              asp                pro                 gly     phe

                                                   100  a   b   c   d   e   f   g   h
humiii  ala arg ASP |ARG GLY GLY ALA VAL SER TYR GLY PHE PHE GLY TYR GLY
kol                 |GLY     HIS GLY PHE CYS SER SER ALA SER CYS PHE GLY

         i   j   k  101|                                          110
humiii  GLY PHE PHE ASP|VAL trp gly gln gly thr leu val thr val ser ser
kol     PRO --- ---    |TYR                     pro
                       ----------------

##################################################################################
The following are proposed Humanized 4D5 sequences; changes in Hum4D5b
and Hum4D5c from Hum4D5a are followed by an asterisk

         1                                          10
humkapI  asp ile gln met thr gln ser pro ser ser leu ser ala ser val gly
Hum4D5a
Hum4D5b
Hum4D5c

                    20                                          30
humkapI  asp arg val thr ile thr cys ARG ALA|SER GLN ASP ILE SER SER TYR|
Hum4D5a                                    |          VAL ASN THR ALA|
Hum4D5b                                    |          VAL ASN THR ALA|
Hum4D5c                                    |          VAL ASN THR ALA|

                                       40
humkapI  LEU ASN trp tyr gln gln lys pro gly lys ala pro lys leu leu ile
Hum4D5a  VAL ALA
Hum4D5b  VAL ALA
Hum4D5c  VAL ALA

         tyr|  50                                                60
humkapI  tyr|ALA ALA SER|SER LEU GLU SER gly val pro ser arg phe ser gly
Hum4D5a    |SER        |PHE
Hum4D5b    |SER        |PHE
Hum4D5c    |SER        |PHE     TYR*

                              70                                        80
humkapI  ser gly ser gly thr asp phe thr leu thr ile ser ser leu gln pro
Hum4D5a      arg
Hum4D5b      gly*
Hum4D5c      arg

                                                  90|
humkapI  glu asp phe ala thr tyr tyr cys GLN GLN|TYR ASN SER LEU PRO TYR|
Hum4D5a                                         |HIS TYR THR THR     PRO|
Hum4D5b                                         |HIS TYR THR THR     PRO|
Hum4D5c                                         |HIS TYR THR THR     PRO|

                    100
humkapI  THR phe gly gln gly thr lys val glu ile lys arg thr
Hum4D5a
Hum4D5b
Hum4D5c
```

V_L

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Witnessed & Understood by me,	Date	Invented by	Date
		Recorded by	